HETERO BIARYL DERIVATIVES AS MATRIX METALLOPROTEINASE INHIBITORS

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of priority from United States Provisional Patent Application Number 60/403,162, filed August 13, 2002.

FIELD OF THE INVENTION

This invention relates to hetero biaryl derivatives which inhibit matrix metalloproteinase enzymes and thus are useful for treating diseases resulting from MMP-mediated tissue breakdown such as heart disease, cardiac insufficiency, inflammatory bowel disease, multiple sclerosis, osteo- and rheumatoid arthritis, arthritis other than osteo- or rheumatoid arthritis, heart failure, age-related macular degeneration, chronic obstructive pulmonary disease, asthma, periodontal diseases, psoriasis, atherosclerosis, and osteoporosis.

BACKGROUND OF THE INVENTION

Matrix metalloproteinases (sometimes referred to as MMPs) are naturally occurring enzymes found in most mammals. Over-expression and activation of MMPs, or an imbalance between MMPs and inhibitors of MMPs, have been suggested as factors in the pathogenesis of diseases characterized by the breakdown of extracellular matrix or connective tissues.

Stromelysin-1 and gelatinase A are members of the MMP family. Other members include fibroblast collagenase (MMP-1), neutrophil collagenase (MMP-8), gelatinase B (92 kDa gelatinase) (MMP-9), stromelysin-2 (MMP-10), stromelysin-3 (MMP-11), matrilysin (MMP-7), collagenase 3 (MMP-13), TNF-alpha converting enzyme (TACE), and other newly discovered membrane-associated matrix metalloproteinases (Sato H., Takino T., Okada Y., Cao J., Shinagawa A., Yamamoto E., and Seiki M., *Nature*, 1994;370:61-65). These

enzymes have been implicated with a number of diseases which result from breakdown of connective tissue, including such diseases as rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal epidermal and gastric ulceration, atherosclerosis, neointimal proliferation which leads to restenosis and ischemic heart failure, and tumor metastasis. A method for preventing and treating these and other diseases is now recognized to be by inhibiting matrix metalloproteinase enzymes, thereby curtailing and/or eliminating the breakdown of connective tissues that results in the disease states.

There is a catalytic zinc domain in matrix metalloproteinases that is typically the focal point for inhibitor design. The modification of substrates by introducing zinc-chelating groups has generated potent inhibitors such as peptide hydroxamates and thiol-containing peptides. Peptide hydroxamates and the natural endogenous inhibitors of MMPs (TIMPs) have been used successfully to treat animal models of cancer and inflammation. MMP inhibitors have also been used to prevent and treat congestive heart failure and other cardiovascular diseases, United States Patent No. 5,948,780.

A major limitation on the use of currently known MMP inhibitors is their lack of specificity for any particular enzyme. Recent data has established that specific MMP enzymes are associated with some diseases, with no effect on others. The MMPs are generally categorized based on their substrate specificity, and indeed the collagenase subfamily of MMP-1, MMP-8, and MMP-13 selectively cleave native interstitial collagens, and thus are associated only with diseases linked to such interstitial collagen tissue. This is evidenced by the recent discovery that MMP-13 alone is over expressed in breast carcinoma, while MMP-1 alone is over expressed in papillary carcinoma (see Chen et al., *J. Am. Chem. Soc.*, 2000;122:9648-9654).

Selective inhibitors of MMP-13 include a compound named WAY-170523, which has been reported by Chen et al., supra., 2000, and other compounds are reported in PCT International Patent Application Publication numbers WO 01/63244; WO 00/09485; WO 01/12611; WO 02/34726; and WO 02/34753, and European Patent Application numbers EP 935,963 and EP 1,138,680. Further, United States Patent number 6,008,243 discloses inhibitors of MMP-13. However, no selective or nonselective inhibitor of MMP-13 has been

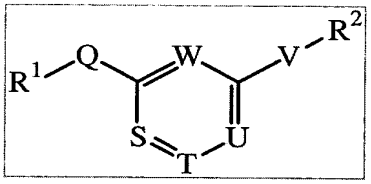
approved and marketed for the treatment of any disease in any mammal. Accordingly, the need continues to find new low molecular weight compounds that are potent and selective MMP inhibitors, and that have an acceptable therapeutic index of toxicity/potency to make them amenable for use clinically in the prevention and treatment of the associated disease states. An object of this invention is to provide a group of selective MMP-13 inhibitor compounds characterized as being hetero biaryl derivatives.

SUMMARY OF THE INVENTION

This invention provides an hetero biaryl derived compound defined by Formula I.

Accordingly, embodiments of the invention include:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 independently are selected from:

H;

C_1-C_6 alkyl;

Substituted C_1-C_6 alkyl;

C_2-C_6 alkenyl;

Substituted C_2-C_6 alkenyl;

C_2-C_6 alkynyl;

Substituted C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

Substituted C_3-C_6 cycloalkyl;

C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl);

Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl);

3- to 6-membered heterocycloalkyl;

Substituted 3- to 6-membered heterocycloalkyl;

3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl);

Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl);

Phenyl-(C_1-C_6 alkylenyl);

Substituted phenyl-(C_1-C_6 alkylenyl);

Naphthyl-(C_1-C_6 alkylenyl);

Substituted naphthyl-(C_1-C_6 alkylenyl);

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5-, 6-, 9-, and 10-membered heteroaryl;

Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

R^3O-(C_1-C_6 alkylenyl);

Substituted R^3O-(C_1-C_6 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl;

Substituted 8- to 10-membered heterobiaryl;

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

wherein R^1 and R^2 are not both selected from:

H;

C_1-C_6 alkyl;

C_2-C_6 alkenyl;

C_2-C_6 alkynyl; and

C_3-C_6 cycloalkyl;

Each R^3 independently is selected from:

H;

C_1-C_6 alkyl;

Substituted C_1-C_6 alkyl;

C_3-C_6 cycloalkyl;

Substituted C_3-C_6 cycloalkyl;

Phenyl-(C_1-C_6 alkylenyl);

Substituted phenyl-(C_1-C_6 alkylenyl);

Naphthyl-(C_1-C_6 alkylenyl);

Substituted naphthyl-(C_1-C_6 alkylenyl);

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5-, 6-, 9-, and 10-membered heteroaryl;

Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

S, T, U, and W each are C-R^4; or

One of S, T, U, and W is N and the other three of S, T, U, and W are C-R^4; or

Two of S, T, U, and W are N and the other two of S, T, U, and W are C-R^4; or

T is C-R^4 and S, U, and W are each N; or

U is C-R^4 and S, T, and W are each N; or

S is C-R^4 and T, U, and W are each N;

Each R^4 independently is selected from:

H;

F;

CH_3;

CF_3;

C(O)H;

CN;

HO;

CH_3O;

$C(F)H_2O$;

$C(H)F_2O$; and

CF_3O;

V is a 5-membered heteroarylenyl; and

Q is selected from:

OCH_2;

$N(R^6)CH_2$;

OC(O);

$CH(R^6)C(O)$;

$OC(NR^6)$;

$CH(R^6)C(NR^6)$;

$N(R^6)C(O)$;

$N(R^6)C(S)$;

$N(R^6)C(NR^6)$;

$N(R^6)CH_2$;

SC(O);

$CH(R^6)C(S)$;

$SC(NR^6)$;

trans-(H)C=C(H);

cis-(H)C=C(H);

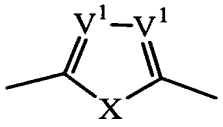
C≡C;

$CH_2C{\equiv}C$;

$C{\equiv}CCH_2$;

$CF_2C{\equiv}C$;

$C{\equiv}CCF_2$;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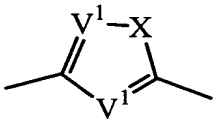
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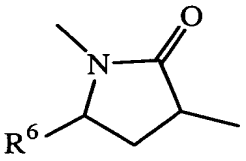
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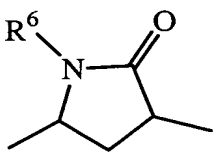
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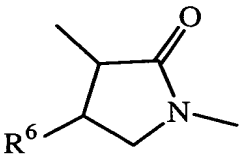
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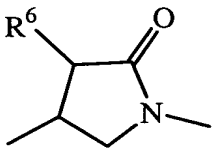
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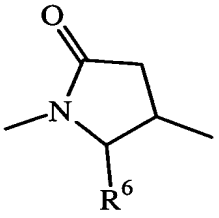

;

or

V is C(O)O, C(S)O, C(O)N(R^5), or C(S)N(R^5); and

Q is selected from:

OCH_2;

N(R^6)CH_2;

CH(R^6)C(O);

OC(NR^6);

CH(R^6)C(NR^6);

N(R^6)C(NR^6);

N(R^6)CH_2;

CH(R^6)C(S);

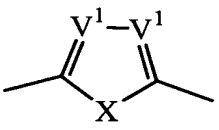
SC(NR^6);

trans-(H)C=C(H);

cis-(H)C=C(H);

$C{\equiv}CH_2$;

$C{\equiv}CCF_2$;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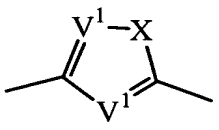
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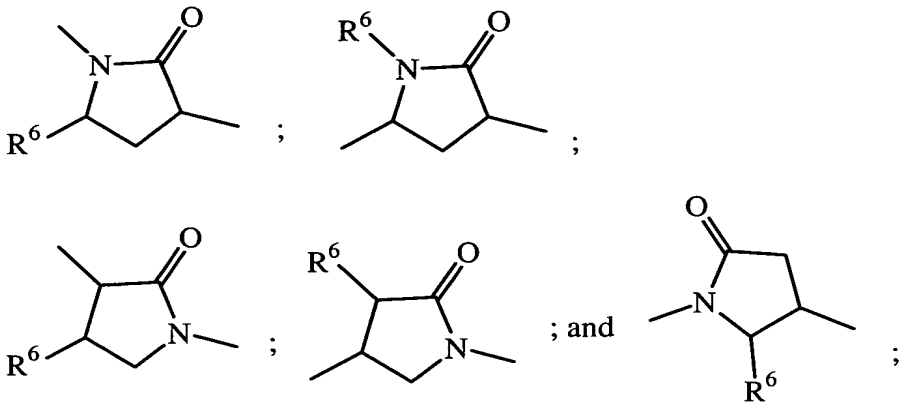


R^5 is H or C_1-C_6 alkyl;

R^6 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl; phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or N(C_1-C_6 alkyl);

Each V^1 is independently C(H) or N;

Each "substituted" group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

C_2-C_6 alkenyl;

C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

C_3-C_6 cycloalkylmethyl;

Phenyl;

Phenylmethyl;

3- to 6-membered heterocycloalkyl;

3- to 6-membered heterocycloalkylmethyl;

cyano;

CF_3;

(C_1-C_6 alkyl)-OC(O);

$HOCH_2$;

(C_1-C_6 alkyl)-OCH_2;

H_2NCH_2;

(C_1-C_6 alkyl)-N(H)CH_2;

(C_1-C_6 alkyl)$_2$-NCH_2;

$N(H)_2C(O)$;

$(C_1$-C_6 alkyl)-$N(H)C(O)$;

$(C_1$-C_6 alkyl)$_2$-$NC(O)$;

$N(H)_2C(O)N(H)$;

$(C_1$-C_6 alkyl)-$N(H)C(O)N(H)$;

$N(H)_2C(O)N(C_1$-C_6 alkyl);

$(C_1$-C_6 alkyl)-$N(H)C(O)N(C_1$-C_6 alkyl);

$(C_1$-C_6 alkyl)$_2$-$NC(O)N(H)$;

$(C_1$-C_6 alkyl)$_2$-$NC(O)N(C_1$-C_6 alkyl);

$N(H)_2C(O)O$;

$(C_1$-C_6 alkyl)-$N(H)C(O)O$;

$(C_1$-C_6 alkyl)$_2$-$NC(O)O$;

HO;

$(C_1$-C_6 alkyl)-O;

CF_3O;

$CF_2(H)O$;

$CF(H)_2O$;

H_2N;

$(C_1$-C_6 alkyl)-N(H);

$(C_1$-C_6 alkyl)$_2$-N;

O_2N;

$(C_1$-C_6 alkyl)-S;

$(C_1$-C_6 alkyl)-S(O);

$(C_1$-C_6 alkyl)-$S(O)_2$;

$(C_1$-C_6 alkyl)$_2$-$NS(O)_2$;

$(C_1$-C_6 alkyl)-$S(O)_2$-$N(H)$-$C(O)$-$(C_1$-C_8 alkylenyl)$_m$; and

$(C_1$-C_6 alkyl)-$C(O)$-$N(H)$-$S(O)_2$-$(C_1$-C_8 alkylenyl)$_m$;

wherein each substituent on a carbon atom may further be independently selected from:

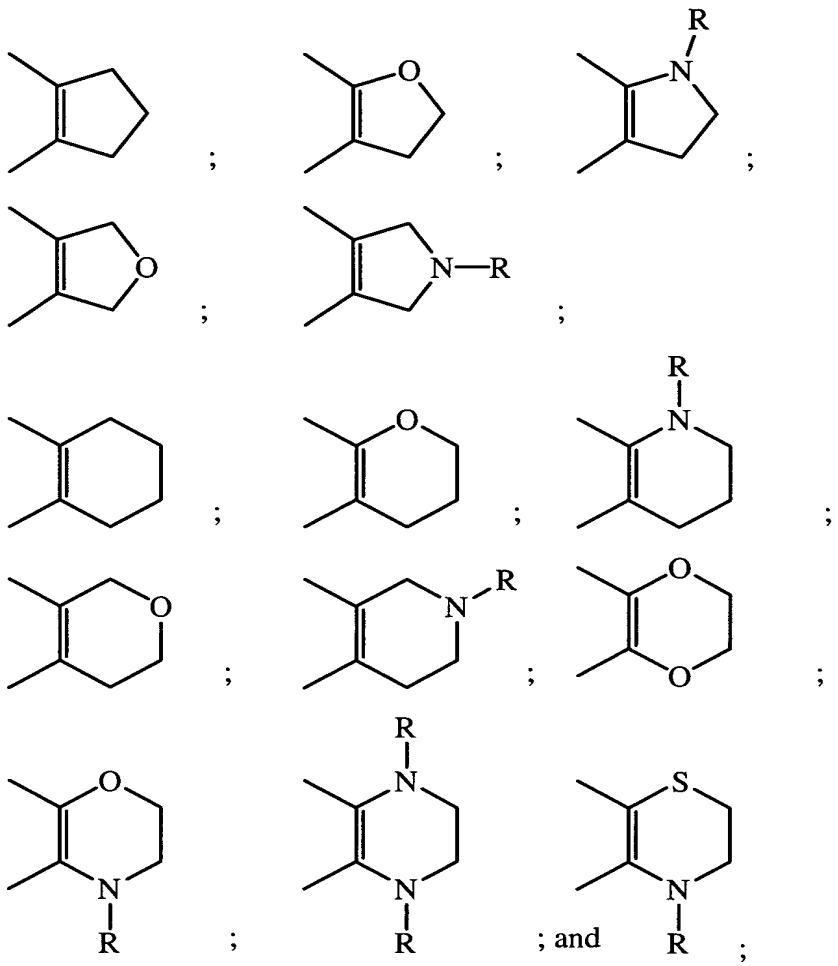
Halo;

HO_2C; and

OCH_2O, wherein each O is bonded to adjacent carbon atoms to form a 5-membered ring;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:



R is H or C_1-C_6 alkyl;

m is an integer of 0 or 1;

wherein each 5-membered heteroarylenyl independently is a 5-membered ring containing carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 NH, 1 N(C_1-C_6 alkyl), and 4 N, wherein the O and S atoms are not both present, and wherein the heteroarylenyl may optionally be unsubstituted or substituted with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl;

wherein each heterocycloalkyl is a ring that contains carbon atoms and 1 or 2 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 2

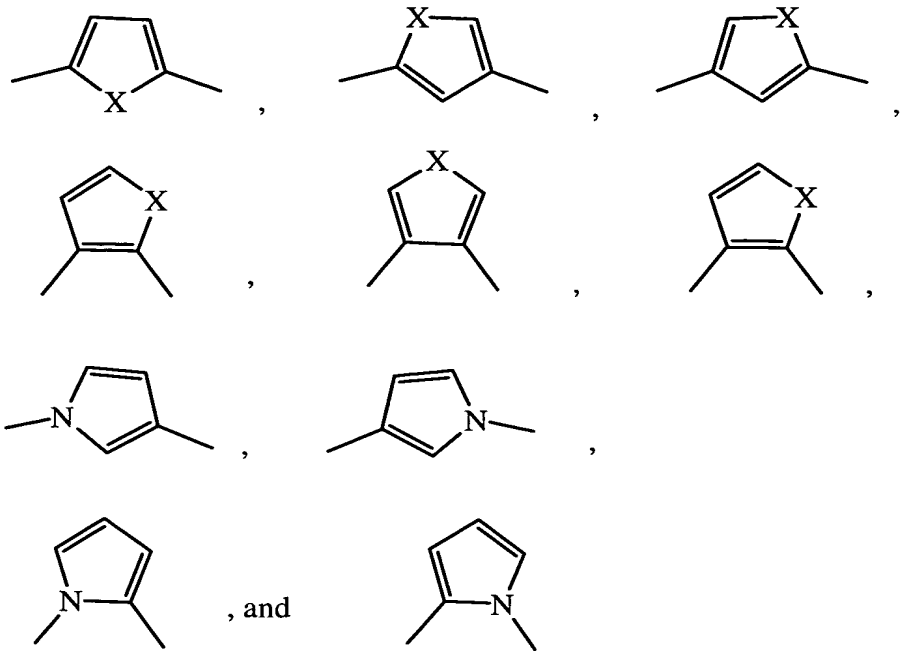
N(H), and 2 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings; and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

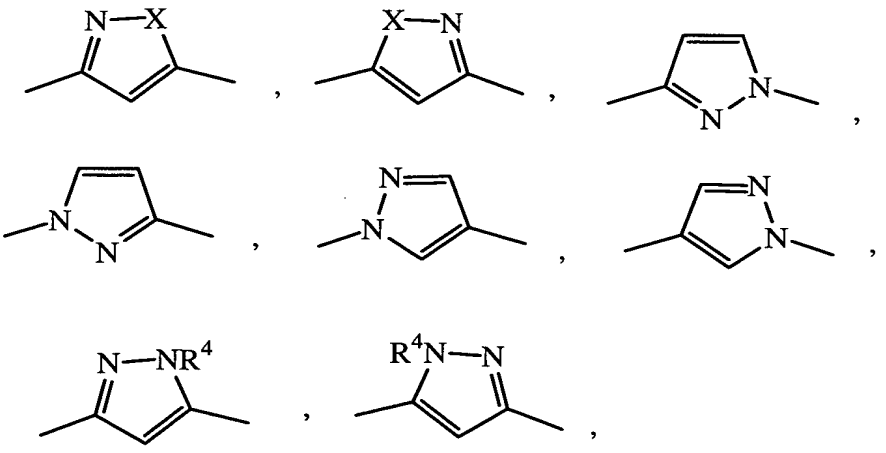
2. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is selected from the groups:

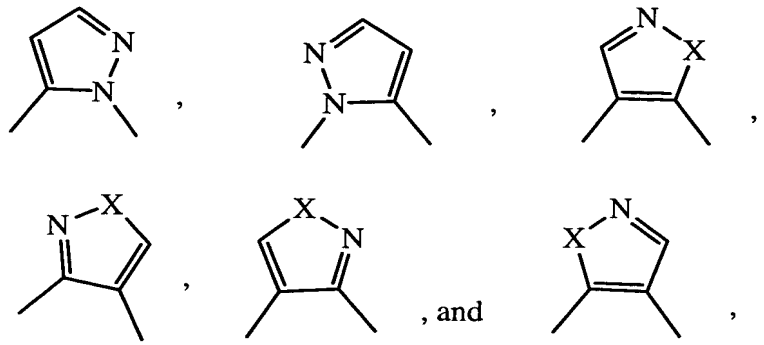


, and

wherein X is O, S, N(H), or N(C_1-C_6 alkyl) and V may optionally be unsubstituted or substituted at C(H) or N(H) with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl.

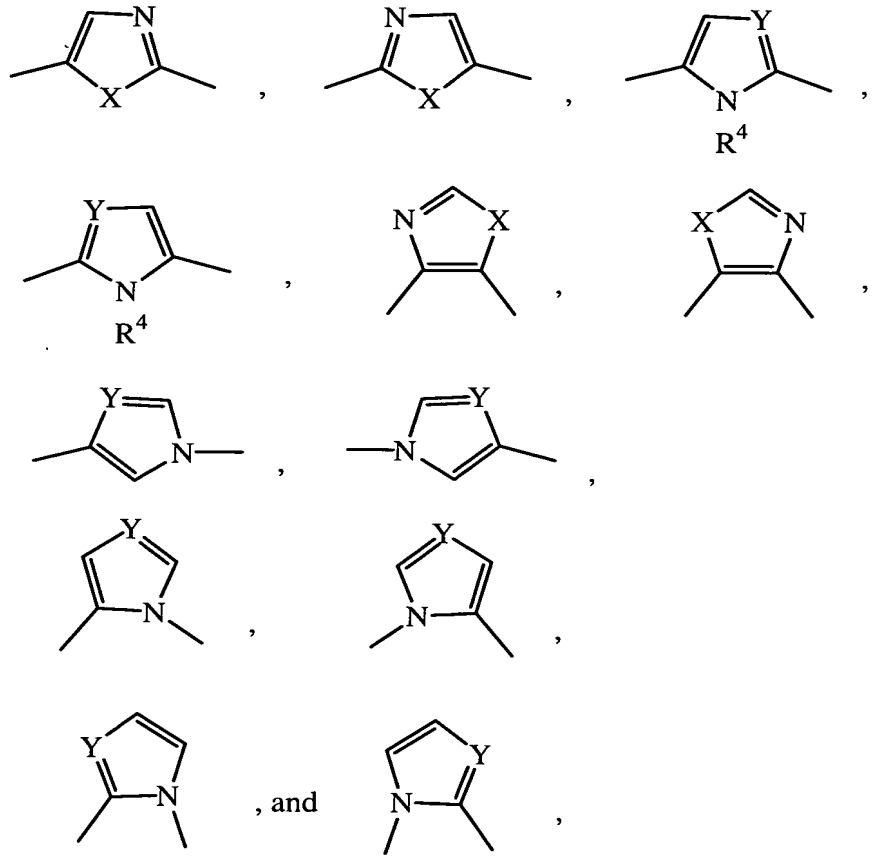
3. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is selected from the groups:





wherein X is O, S, N(H), or N(C_1-C_6 alkyl), R^4 is H or C_1-C_6 alkyl, and V may optionally be unsubstituted or substituted at C(H) or N(H) with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl.

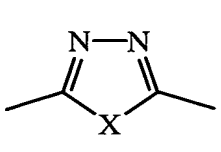
4. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is selected from the groups:



wherein X is O, S, N(H), or N(C_1-C_6 alkyl), Y is O, S, or N, and R^4 is H or C_1-C_6 alkyl, and V may optionally be unsubstituted or substituted at C(H) or N(H) with

1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl.

5. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is selected from the groups: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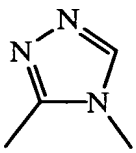
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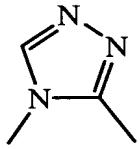
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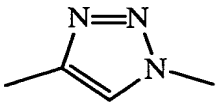
wherein X is O, S, N(H), or N(C_1-C_6 alkyl), and V may optionally be unsubstituted or substituted at C(H) with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl.

6. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is selected from the groups: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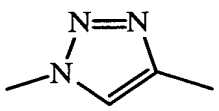
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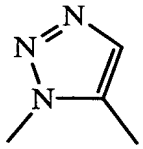
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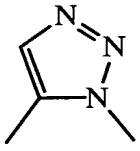
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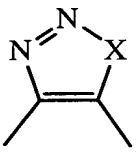
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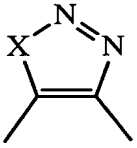
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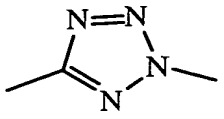
wherein X is O, S, N(H), or N(C_1-C_6 alkyl), and V may optionally be unsubstituted or substituted at C(H) with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl.

7. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is selected from the groups: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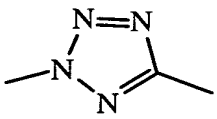
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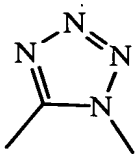
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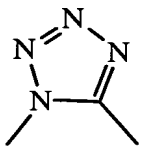
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8. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is $C(O)N(R^5)$.

9. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein V is C(O)O.

10. The compound according to any one of Embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Q is C≡C, $CH_2C{\equiv}C$, or $CF_2C{\equiv}C$.

11. The compound according to any one of Embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Q is OC(O).

12. The compound according to any one of Embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^6)C(O)$.

13. The compound according to any one of Embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Q is N(H)C(O).

14. The compound according to any one of Embodiments 1 to 9, or a pharmaceutically acceptable salt thereof, wherein Q is $N(H)CH_2$ or $N(CH_3)CH_2$.

15. The compound according to any one of Embodiments 1 to 9, or a pharmaceutically acceptable salt thereof, wherein Q is $C{\equiv}CCH_2$ or $C{\equiv}CCF_2$.

16. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

Phenyl-(C_1-C_6 alkylenyl); and

Substituted phenyl-(C_1-C_6 alkylenyl);

wherein each group and each substituent is independently selected.

17. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2 are independently selected from:

Phenyl-(C_1-C_6 alkylenyl); and

Substituted phenyl-(C_1-C_6 alkylenyl);

wherein each group and each substituent is independently selected.

18. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

19. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2 is independently selected from:

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

20. The compound according to any one of Embodiments 1 to 15, 18, and 19, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

5-, 6-, and 9-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-membered heteroaryl-(C_1-C_6 alkylenyl);

wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9-membered heteroaryl is 6,5-fused bicyclic ring, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

21. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl); and

Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl);

wherein each heterocycloalkyl is a ring that contains carbon atoms and 1 or 2 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 2 N(H), and 2 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or

optionally contains one carbon-carbon or carbon-nitrogen double bond; and

wherein each group and each substituent recited above is independently selected.

22. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_2-C_6 alkenyl; and

Substituted C_2-C_6 alkenyl.

23. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_1-C_6 alkyl; and

Substituted C_1-C_6 alkyl.

24. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_2-C_6 alkynyl; and

Substituted C_2-C_6 alkynyl.

25. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl); and

Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl).

26. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_3-C_6 cycloalkyl;

Substituted C_3-C_6 cycloalkyl

3- to 6-membered heterocycloalkyl;
Substituted 3- to 6-membered heterocycloalkyl;
Phenyl;
Substituted phenyl;
Naphthyl;
Substituted naphthyl;
5-, 6-, 9-, and 10-membered heteroaryl; and
Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

27. The compound according to any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is H.

28. The compound according to any one of Embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein each C_1-C_6 alkylenyl is CH_2, $C(CH_3)_2$, C(=O), or CF_2.

29. The compound according to any one of Embodiments 1 to 28, or a pharmaceutically acceptable salt thereof, wherein each C_1-C_6 alkylenyl is CH_2.

30. The compound according to any one of Embodiments 1 to 29, or a pharmaceutically acceptable salt thereof, wherein at least one substituent is selected from the groups:

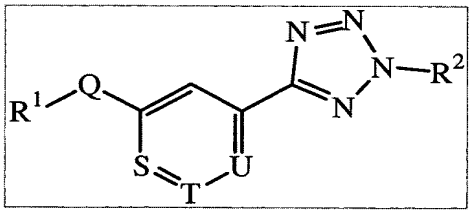
CO_2H;
CO_2CH_3;
CH_3O;
F;
Cl;
CN;
CF_3;
$CH_3S(O)_2$;
CH_3; or

wherein at least two substituents are Cl and F, 2 F, or OCH_2O, wherein each O is bonded to adjacent carbon atoms to form a 5-membered ring.

31. The compound according to any one of Embodiments 1 to 30, or a pharmaceutically acceptable salt thereof, wherein S, T, U, and W are each CH.

32. The compound according to any one of Embodiments 1 to 30, or a pharmaceutically acceptable salt thereof, wherein S is C-OCH_3 and T, U, and W are each CH.

33. A compound of Formula II



II

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 independently are selected from:

H;

C_1-C_6 alkyl;

Substituted C_1-C_6 alkyl;

C_2-C_6 alkenyl;

Substituted C_2-C_6 alkenyl;

C_2-C_6 alkynyl;

Substituted C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

Substituted C_3-C_6 cycloalkyl;

C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl);

Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl);

3- to 6-membered heterocycloalkyl;

Substituted 3- to 6-membered heterocycloalkyl;

3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl);

Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl);

Phenyl-(C_1-C_6 alkylenyl);

Substituted phenyl-(C_1-C_6 alkylenyl);

Naphthyl-(C_1-C_6 alkylenyl);

Substituted naphthyl-(C_1-C_6 alkylenyl);

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5-, 6-, 9-, and 10-membered heteroaryl;

Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

R^3O-(C_1-C_6 alkylenyl); and

Substituted R^3O-(C_1-C_6 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl;

Substituted 8- to 10-membered heterobiaryl;

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

wherein R^1 and R^2 are not both selected from:

H;

C_1-C_6 alkyl;

C_2-C_6 alkenyl;

C_2-C_6 alkynyl; and

C_3-C_6 cycloalkyl;

Each R^3 independently is selected from:

H;

C_1-C_6 alkyl;

Substituted C_1-C_6 alkyl;

C_3-C_6 cycloalkyl;

Substituted C_3-C_6 cycloalkyl;

Phenyl-(C_1-C_6 alkylenyl);

Substituted phenyl-(C_1-C_6 alkylenyl);

Naphthyl-(C_1-C_6 alkylenyl);

Substituted naphthyl-(C_1-C_6 alkylenyl);

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5-, 6-, 9-, and 10-membered heteroaryl;

Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

S, T, and U each are C-R^4; or

One of S, T, and U is N and the other two of S, T, and U are C-R^4; or

Two of S, T, and U are N and the other one of S, T, and U is C-R^4;

Each R^4 independently is selected from:

H;

F;

CH_3;

CF_3;

C(O)H;

CN;

HO;

CH_3O;

$C(F)H_2O$;

$C(H)F_2O$; and

CF_3O;

Q is selected from:

OCH_2;

$N(R^6)CH_2$;

OC(O);

$CH(R^6)C(O)$;

$OC(NR^6)$;

$CH(R^6)C(NR^6)$;

$N(R^6)C(O)$;

$N(R^6)C(NR^6)$;

$N(R^6)CH_2$;

SC(O);

$CH(R^6)C(S)$;

$SC(NR^6)$;

trans-(H)C=C(H);

cis-(H)C=C(H);

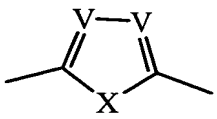
C≡C;

$CH_2C{\equiv}C$;

$C{\equiv}CCH_2$;

$CF_2C{\equiv}C$;

$C{\equiv}CCF_2$;



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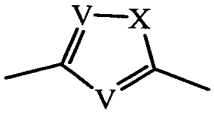

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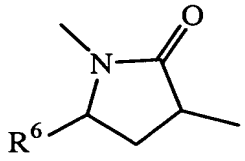
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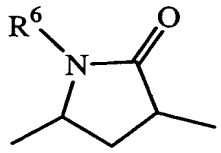
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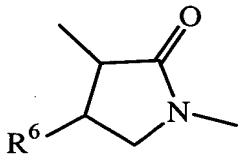
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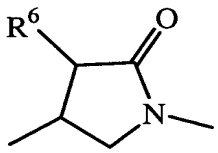
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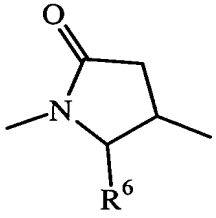

; or

R^6 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl; phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or N(C_1-C_6 alkyl);

Each V^1 is independently C(H) or N;

Each "substituted" group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

C_2-C_6 alkenyl;

C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

C_3-C_6 cycloalkylmethyl;

Phenyl;

Phenylmethyl;

3- to 6-membered heterocycloalkyl;

3- to 6-membered heterocycloalkylmethyl;

cyano;

CF_3;

(C_1-C_6 alkyl)-OC(O);

$HOCH_2$;

(C_1-C_6 alkyl)-OCH_2;

H_2NCH_2;

(C_1-C_6 alkyl)-N(H)CH_2;

(C_1-C_6 alkyl)$_2$-NCH_2;

$N(H)_2C(O)$;

(C_1-C_6 alkyl)-N(H)C(O);

(C_1-C_6 alkyl)$_2$-NC(O);

$N(H)_2C(O)N(H)$;

(C_1-C_6 alkyl)-N(H)C(O)N(H);

$N(H)_2C(O)N(C_1$-C_6 alkyl);

(C_1-C_6 alkyl)-N(H)C(O)N(C_1-C_6 alkyl);

(C_1-C_6 alkyl)$_2$-NC(O)N(H);

(C_1-C_6 alkyl)$_2$-NC(O)N(C_1-C_6 alkyl);

$N(H)_2C(O)O$;

(C_1-C_6 alkyl)-N(H)C(O)O;

(C_1-C_6 alkyl)$_2$-NC(O)O;

HO;

(C_1-C_6 alkyl)-O;

CF_3O;

$CF_2(H)O$;

$CF(H)_2O$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

O_2N;

(C_1-C_6 alkyl)-S;

(C_1-C_6 alkyl)-S(O);

(C_1-C_6 alkyl)-$S(O)_2$;

(C_1-C_6 alkyl)$_2$-$NS(O)_2$;

(C_1-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$; and

(C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

wherein each substituent on a carbon atom may further be independently selected from:

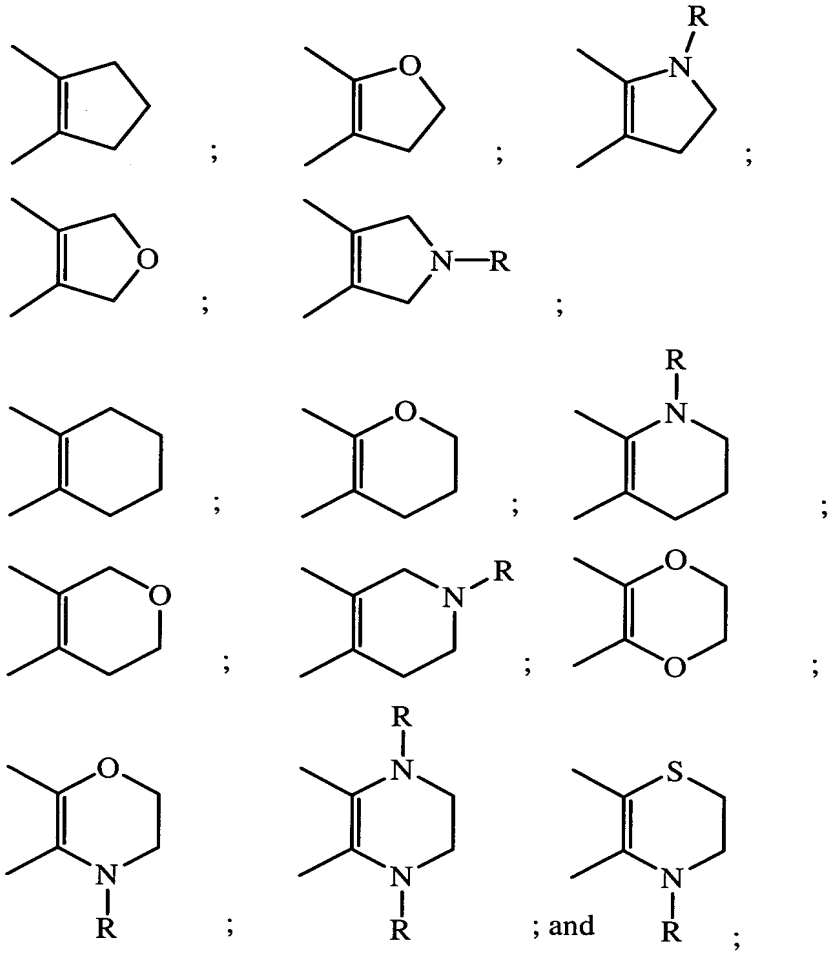
Halo;

HO_2C; and

OCH_2O, wherein each O is bonded to adjacent carbon atoms to form a 5-membered ring;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:



; and

R is H or C_1-C_6 alkyl;

wherein each 5-membered heteroarylenyl independently is a 5-membered ring containing carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 NH, 1 N(C_1-C_6 alkyl), and 4 N, wherein the O and S atoms are not both present, and wherein the heteroarylenyl may optionally be unsubstituted or substituted with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl;

wherein each heterocycloalkyl is a ring that contains carbon atoms and 1 or 2 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 2 N(H), and 2 N(C_1-C_6 alkyl), and wherein when two O atoms or one O

atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings; and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

34. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is OC(O).

35. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is OCH_2.

36. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^6)C(O)$.

37. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is N(H)C(O).

38. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^6)CH_2$.

39. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is $N(H)CH_2$.

40. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is $N(CH_3)CH_2$.

41. The compound according to Embodiment 33, or a pharmaceutically acceptable salt thereof, wherein Q is $C{\equiv}C$, $CH_2C{\equiv}C$, $C{\equiv}CCH_2$, $CF_2C{\equiv}C$, or $C{\equiv}CCF_2$.

42. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

Phenyl-(C_1-C_6 alkylenyl); and

Substituted phenyl-(C_1-C_6 alkylenyl);

wherein each group and each substituent is independently selected.

43. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2 are independently selected from:

Phenyl-(C_1-C_6 alkylenyl); and

Substituted phenyl-(C_1-C_6 alkylenyl);

wherein each group and each substituent is independently selected.

44. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings,

respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

45. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2 is independently selected from:

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

46. The compound according to any one of Embodiments 33 to 41, 44, and 45, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2, is independently selected from:

5-, 6-, and 9-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-membered heteroaryl-(C_1-C_6 alkylenyl);

wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9-membered heteroaryl is 6,5-fused bicyclic ring, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

47. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl); and

Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl);

wherein each heterocycloalkyl is a ring that contains carbon atoms and 1 or 2 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 2 N(H), and 2 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond; and

wherein each group and each substituent recited above is independently selected.

48. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_2-C_6 alkenyl; and

Substituted C_2-C_6 alkenyl.

49. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_1-C_6 alkyl; and

Substituted C_1-C_6 alkyl.

50. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_2-C_6 alkynyl; and

Substituted C_2-C_6 alkynyl.

51. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 and R^2 is independently selected from:

C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl); and

Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl).

52. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is independently selected from:

C_3-C_6 cycloalkyl;

Substituted C_3-C_6 cycloalkyl

3- to 6-membered heterocycloalkyl;

Substituted 3- to 6-membered heterocycloalkyl;

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5-, 6-, 9-, and 10-membered heteroaryl; and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

53. The compound according to any one of Embodiments 33 to 41, or a pharmaceutically acceptable salt thereof, wherein one of R^1 and R^2 is H.

54. The compound according to any one of Embodiments 33 to 53, or a pharmaceutically acceptable salt thereof, wherein each C_1-C_6 alkylenyl is CH_2, $C(CH_3)_2$, C(=O), or CF_2.

55. The compound according to any one of Embodiments 33 to 54, or a pharmaceutically acceptable salt thereof, wherein each C_1-C_6 alkylenyl is CH_2.

56. The compound according to any one of Embodiments 33 to 55, or a pharmaceutically acceptable salt thereof, wherein at least one substituent is selected from the groups:

CO_2H;

CO_2CH_3;

CH_3O;

F;

Cl;

CN;

CF_3;

$CH_3S(O)_2$;

CH_3; or

wherein at least two substituents are Cl and F, 2 F, or OCH_2O, wherein each O is bonded to adjacent carbon atoms to form a 5-membered ring.

57. The compound according to any one of Embodiments 33 to 56, or a pharmaceutically acceptable salt thereof, wherein S, T, and U are each CH.

58. The compound according to any one of Embodiments 33 to 57, or a pharmaceutically acceptable salt thereof, wherein S is C-OCH_3 and T and U are each CH.

59. The compound according to Embodiment 33, selected from:

4-({3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester;

4-({3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid;

4-({3-[2-(3-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester;

4-({3-[2-(3-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid;

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(4-morpholin-4-ylmethyl-benzyl)-benzamide;

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(3-trifluoromethyl-benzyl)-benzamide;

N-Benzyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide;

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(2-trifluoromethyl-benzyl)-benzamide; and

N-(4-Methoxy-benzyl)-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide; or

a pharmaceutically acceptable salt thereof.

60. The compound according to Embodiment 33, selected from:

4-({3-[2-(4-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester;

4-({3-[2-(4-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid;

4-({3-[2-(3-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester;

4-({3-[2-(3-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid;

N-(3-Chloro-4-fluoro-benzyl)-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide;

N-(2,3-Difluoro-benzyl)-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide; and

N-(4-Fluoro-benzyl)-2-methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide; or

a pharmaceutically acceptable salt thereof.

61. The compound according to Embodiment 33, named:

N-Benzyl-3-[2-(4-cyano-benzyl)-2H-tetrazol-5-yl]-benzamide; or

a pharmaceutically acceptable salt thereof.

62. The compound according to Embodiment 33, named:

4-{[3-(2-Thiazol-2-ylmethyl-2H-tetrazol-5-yl)-benzoylamino]-methyl}-benzoic acid methyl ester; or

a pharmaceutically acceptable salt thereof.

63. The compound according to Embodiment 33, selected from:

4-{[3-(2-But-2-enyl-2H-tetrazol-5-yl)-benzoylamino]-methyl}benzoic acid methyl ester;

N-Benzyl-3-(2-but-2-enyl-2H-tetrazol-5-yl)-benzamide; and

3-(2-But-2-enyl-2H-tetrazol-5-yl)-N-(3-methoxy-benzyl)-benzamide; or

a pharmaceutically acceptable salt thereof.

64. The compound according to Embodiment 33, selected from:

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-thiazol-2-ylmethyl-benzamide;

N-2,1,3-Benzothiadiazol-5-ylmethyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide;

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(2-methoxy-pyridin-4-ylmethyl)-benzamide;

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-pyridin-4-ylmethyl-benzamide;

N-1,3-Benzodioxol-5-ylmethyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide; and

N-Furan-2-ylmethyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide; or

a pharmaceutically acceptable salt thereof.

65. The compound according to Embodiment 33, selected from:

4-(5-{3-[(Pyridin-4-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid;

4-(5-{3-[(Pyridin-3-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid; and

4-(5-{3-[(2-Methoxy-pyridin-4-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid; or

a pharmaceutically acceptable salt thereof.

66. The compound according to Embodiment 33, named:

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(2-pyridin-4-yl-ethyl)-benzamide; or

a pharmaceutically acceptable salt thereof.

67. The compound according to Embodiment 33, named:
N-Isopropyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide; or
a pharmaceutically acceptable salt thereof.

68. The compound according to Embodiment 33, named:
3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(1-phenyl-ethyl)-benzamide; or
a pharmaceutically acceptable salt thereof.

69. The compound according to Embodiment 33, named:
4-(5-{3-[(Methyl-pyridin-3-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid; or
a pharmaceutically acceptable salt thereof.

70. The compound according to Embodiment 33, selected from:
4-({2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid;
4-({2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid; and
2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-N-(4-trifluoromethyl-benzyl)-benzamide; or
a pharmaceutically acceptable salt thereof.

71. The compound according to Embodiment 33, named:
Benzyl{3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzyl}-amine hydrochloride; or
a pharmaceutically acceptable salt thereof.

72. The compound according to Embodiment 33, selected from:
(4-Methanesulfonyl-benzyl)-{3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzyl}-amine; and

4-({3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5yl]-benzylamino}-methyl)-benzoic acid; or

a pharmaceutically acceptable salt thereof.

73. The compound according to Embodiment 33, selected from:

4-{3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzyloxymethyl}-benzoic acid; and

4-{3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzyloxy}-benzoic acid; or

a pharmaceutically acceptable salt thereof.

74. The compound according to Embodiment 33, selected from:

4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid; and

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid; or

a pharmaceutically acceptable salt thereof.

75. The compound according to Embodiment 33, named:

4-{5-[3-(3-Methyl-3-phenyl-but-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid; or

a pharmaceutically acceptable salt thereof.

76. The compound according to Embodiment 33, named:

4-{5-[3-(3-Imidazol-1-yl-prop-1-ynyl)-phenyl]-terazol-2-ylmethyl}-benzoic acid; or

a pharmaceutically acceptable salt thereof.

Another aspect of this invention is a compound of Formula I selected from:

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid;

[4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-phenyl]-acetic acid;

1-[4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-phenyl]-cyclopropanecarboxylic acid;

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzamide;

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-2-methyl-benzoic acid; and

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-cyclohexanecarboxylic acid; or

a pharmaceutically acceptable salt thereof.

Another aspect of this invention is a compound of Formula I selected from:

2-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-oxazole-4-carboxylic acid; and

2-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-thiazole-4-carboxylic acid; or

a pharmaceutically acceptable salt thereof.

Another aspect of this invention is a compound of Formula I selected from:

4-{5-[2-(4-Fluoro-benzylcarbamoyl)-6-methyl-pyridin-4-yl]-tetrazol-2-ylmethyl}-benzoic acid;

4-{5-[2-(3,4-Difluoro-benzylcarbamoyl)-pyridin-4-yl]-tetrazol-2-ylmethyl}-benzoic acid;

4-{5-[2-(3,4-Difluoro-benzylcarbamoyl)-6-methyl-pyridin-4-yl]-tetrazol-2-ylmethyl}-benzoic acid; and

4-(5-{2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-carbamoyl]-pyridin-4-yl}-tetrazol-2-ylmethyl)-benzoic acid; or

a pharmaceutically acceptable salt thereof.

Another aspect of this invention is a compound of Formula I selected from:

4-(5-{3-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-yl)-benzoic acid;

4-(5-{3-[5-(4-Chloro-phenyl)-[1,3,4]thiadiazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-ylmethyl)-benzoic acid;

4-(2-{3-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-oxazol-5-yl)-benzoic acid;

4-(2-{3-[5-(4-Chloro-phenyl)-oxazol-2-yl]-phenyl}-oxazol-5-yl)-benzoic acid;

4-(5-{3-[5-(4-Chloro-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-ylmethyl)-benzoic acid;

4-(5-{3-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-yl)-benzoic acid;

4-(5-{3-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid;

4-(5-{3-[5-(4-Chloro-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-yl)-benzoic acid;

4-(5-{3-[5-(4-Chloro-phenyl)-[1,3,4]thiadiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-yl)-benzoic acid;

4-(2-{3-[5-(4-Chloro-phenyl)-[1,3,4]thiadiazol-2-yl]-phenyl}-oxazol-5-yl)-benzoic acid; or

a pharmaceutically acceptable salt thereof.

77. A pharmaceutical composition, comprising a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

78. The pharmaceutical composition according to Embodiment 77, comprising a compound of Formula I according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

79. A method for inhibiting an MMP-13 enzyme in an animal, comprising administering to the animal an MMP-13 inhibiting amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

80. The method according to Embodiment 79, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

81. A method for treating a disease mediated by an MMP-13 enzyme, comprising administering to a patient suffering from such a disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

82. The method according to Embodiment 81, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

83. A method for treating arthritis, comprising administering to a patient suffering from an arthritis disease a nontoxic antiarthritic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

84. The method according to Embodiment 83, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

85. A method for treating osteoarthritis, comprising administering to a patient suffering from osteoarthritis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

86. The method according to Embodiment 85, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

87. A method for treating rheumatoid arthritis, comprising administering to a patient suffering from rheumatoid arthritis a nontoxic effective amount of a

compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

88. The method according to Embodiment 87, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

89. A method for treating psoriatic arthritis, comprising administering to a patient suffering from psoriatic arthritis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

90. The method according to Embodiment 89, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

91. A method for treating a cancer, comprising administering to a patient suffering from a cancer a nontoxic anti-cancer effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

92. The method according to Embodiment 91, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

93. A method for treating breast carcinoma, comprising administering to a patient suffering from breast carcinoma a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

94. The method according to Embodiment 93, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

95. A method for treating atherosclerosis, comprising administering to a patient suffering from atherosclerosis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

96. The method according to Embodiment 95, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

97. A method for treating inflammation, comprising administering to a patient suffering from inflammation a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

98. The method according to Embodiment 97, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

99. A method for treating heart failure, comprising administering to a patient suffering from heart failure a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

100. The method according to Embodiment 99, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

101. A method for treating age-related macular degeneration, comprising administering to a patient suffering from age-related macular degeneration a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

102. The method according to Embodiment 101, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

103. A method for treating chronic obstructive pulmonary disease, comprising administering to a patient suffering from chronic obstructive pulmonary disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

104. The method according to Embodiment 103, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

105. A method for treating heart disease, comprising administering to a patient suffering from heart disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

106. The method according to Embodiment 105, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

107. A method for treating multiple sclerosis, comprising administering to a patient suffering from multiple sclerosis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

108. The method according to Embodiment 107, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

109. A method for treating psoriasis, comprising administering to a patient suffering from psoriasis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

110. The method according to Embodiment 109, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

111. A method for treating asthma, comprising administering to a patient suffering from asthma a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

112. The method according to Embodiment 111, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

113. A method for treating cardiac insufficiency, comprising administering to a patient suffering from cardiac insufficiency a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

114. The method according to Embodiment 113, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

115. A method for treating inflammatory bowel disease, comprising administering to a patient suffering from inflammatory bowel disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

116. The method according to Embodiment 115, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

117. A method for treating osteoporosis, comprising administering to a patient suffering from osteoporosis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

118. The method according to Embodiment 117, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

119. A method for treating periodontal diseases, comprising administering to a patient suffering from periodontal diseases a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

120. The method according to Embodiment 119, wherein the compound of Formula I is according to any one of Embodiments 2 to 76, or a pharmaceutically acceptable salt thereof.

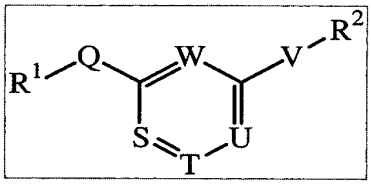
121. The method according to any one of Embodiments 79 to 120, wherein the compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition according to Embodiment 77 or 78.

122. The compound according to Embodiment 1, wherein S is N and Q is N(H)C(O).

123. The compound according to Embodiment 1, wherein W is N and Q is N(H)C(O).

Another aspect of this invention is a method of synthesizing a compound of Formula I according to the methods described below.

Another aspect of this invention is a compound of Formula Ia



Ia

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^2 independently are selected from: Substituted C_1-C_6 alkyl, Substituted C_2-C_6 alkenyl, Substituted C_2-C_6 alkynyl, Substituted C_3-C_6 cycloalkyl, Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl), Substituted 3- to 6-membered heterocycloalkyl, Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl), Phenyl-(C_1-C_6 alkylenyl), Substituted phenyl-(C_1-C_6 alkylenyl), 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl), Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl), Phenyl, Substituted phenyl, 5-, 6-, 9-, and 10-membered heteroaryl, Substituted 5-, 6-, 9-, and 10-membered heteroaryl, R^3O-(C_1-C_6 alkylenyl), Substituted R^3O-(C_1-C_6 alkylenyl), Phenyl, Substituted phenyl, 5- or 6-membered heteroaryl, Substituted 5- or 6-membered heteroaryl, 8- to 10-membered heterobiaryl, Substituted 8- to 10-membered heterobiaryl, Phenyl-O-(C_1-C_8 alkylenyl), Substituted phenyl-O-(C_1-C_8 alkylenyl), Phenyl-S-(C_1-C_8 alkylenyl), Substituted phenyl-S-(C_1-C_8 alkylenyl), Phenyl-S(O)-(C_1-C_8 alkylenyl), Substituted phenyl-S(O)-(C_1-C_8 alkylenyl), Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl), and Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

Each R^3 independently is selected from: Substituted C_1-C_6 alkyl, Substituted C_3-C_6 cycloalkyl, Phenyl-(C_1-C_6 alkylenyl), Substituted phenyl-(C_1-C_6 alkylenyl), 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl), Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl), Phenyl, Substituted phenyl, 5-, 6-, 9-, and 10-membered heteroaryl, Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

S, T, U, and W each are C-R^4; or

One of S, T, U, and W is N and the other three of S, T, U, and W are C-R^4; or

Two of S, T, U, and W are N and the other two of S, T, U, and W are C-R^4; or

T is C-R^4 and S, U, and W are each N; or

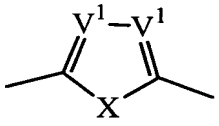
U is C-R^4 and S, T, and W are each N; or

S is C-R^4 and T, U, and W are each N;

Each R^4 independently is selected from: H, F, CH_3, CF_3, C(O)H, CN, HO, CH_3O, $C(F)H_2O$, $C(H)F_2O$, and CF_3O;

V is a 5-membered heteroarylenyl; and

Q is selected from: OCH_2, $N(R^6)CH_2$, OC(O), $CH(R^6)C(O)$, $OC(NR^6)$, $CH(R^6)C(NR^6)$, $N(R^6)C(O)$, $N(R^6)C(S)$, $N(R^6)C(NR^6)$, $N(R^6)CH_2$, SC(O), $CH(R^6)C(S)$, $SC(NR^6)$, trans-(H)C=C(H), cis-(H)C=C(H), C≡C, $CH_2C{\equiv}C$, $C{\equiv}CCH_2$, $CF_2C{\equiv}C$, $C{\equiv}CCF_2$,



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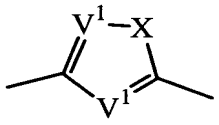

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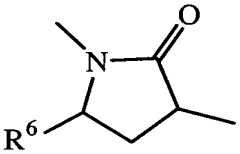

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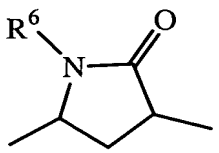

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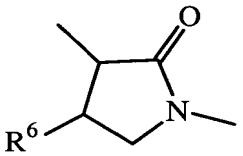

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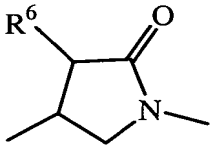

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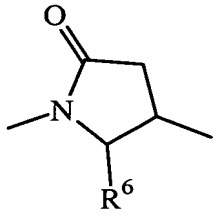
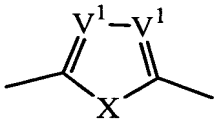


;

or

V is C(O)O, C(S)O, $C(O)N(R^5)$, or $C(S)N(R^5)$; and

Q is selected from: OCH_2, $N(R^6)CH_2$, $CH(R^6)C(O)$, $OC(NR^6)$, $CH(R^6)C(NR^6)$, $N(R^6)C(NR^6)$, $N(R^6)CH_2$, $CH(R^6)C(S)$, $SC(NR^6)$, trans-(H)C=C(H), cis-(H)C=C(H), $C{\equiv}CCH_2$, $C{\equiv}CCF_2$,



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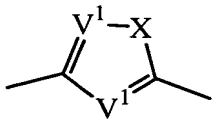

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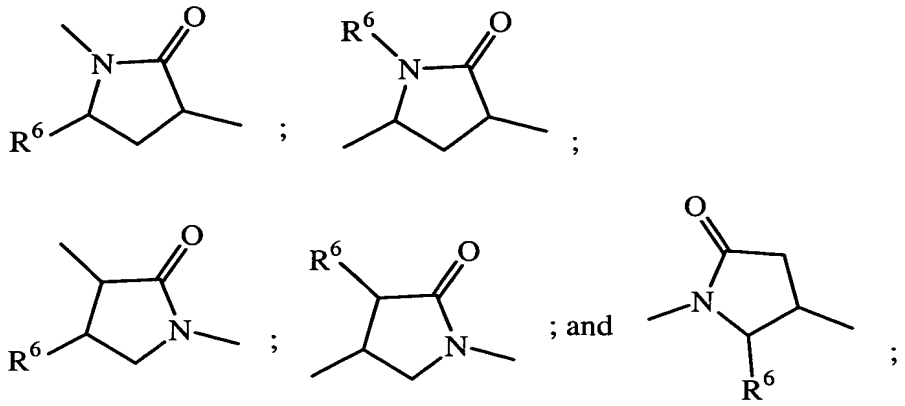


R^5 is H or C_1-C_6 alkyl;

R^6 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl; phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or N(C_1-C_6 alkyl);

Each V^1 is independently C(H) or N;

Each "substituted" group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, Phenyl, Phenylmethyl, 3- to 6-membered heterocycloalkyl, 3- to 6-membered heterocycloalkylmethyl, cyano, CF_3, (C_1-C_6 alkyl)-OC(O), $HOCH_2$, (C_1-C_6 alkyl)-OCH_2, H_2NCH_2, (C_1-C_6 alkyl)-N(H)CH_2, (C_1-C_6 alkyl)$_2$-NCH_2, N(H)$_2$C(O), (C_1-C_6 alkyl)-N(H)C(O), (C_1-C_6 alkyl)$_2$-NC(O), N(H)$_2$C(O)N(H), (C_1-C_6 alkyl)-N(H)C(O)N(H), N(H)$_2$C(O)N(C_1-C_6 alkyl), (C_1-C_6 alkyl)-N(H)C(O)N(C_1-C_6 alkyl), (C_1-C_6 alkyl)$_2$-NC(O)N(H), (C_1-C_6 alkyl)$_2$-NC(O)N(C_1-C_6 alkyl), N(H)$_2$C(O)O, (C_1-C_6 alkyl)-N(H)C(O)O, (C_1-C_6 alkyl)$_2$-NC(O)O, HO, (C_1-C_6 alkyl)-O, CF_3O, $CF_2(H)O$, $CF(H)_2O$, H_2N, (C_1-C_6 alkyl)-N(H), (C_1-C_6 alkyl)$_2$-N, O_2N, (C_1-C_6 alkyl)-S, (C_1-C_6 alkyl)-S(O), (C_1-C_6 alkyl)-$S(O)_2$, (C_1-C_6 alkyl)$_2$-NS(O), (C_1-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$, (C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$, HO-C(=O)-(C_1-C_3 alkylenyl), HO-C(=O)-(C_3-C_6 cycloalkylen-1-yl), Phenyl substituted with 1 or two substituents selected from F, Cl, OH, OCH_3, C≡N, COOH, $COOCH_3$, C(=O)CH_3, and CF_3, 5- or 6-membered heteroaryl, 5- or 6-membered heteroaryl substituted with 1 substituent

selected from F, Cl, OH, OCH_3, C≡N, COOH, $COOCH_3$, $C(=O)CH_3$, and CF_3, SO_3H, PO_3H_2, and R^7R^{7a}-$(J)_m$-$N(H)CH_2$, wherein m is an integer of 0 or 1; J is N-C(=O); and R^7 and R^{7a} are independently selected from hydrogen, C_1-C_6 alkyl, (C_1-C_6 alkyl)-C(=O), C_1-C_6 alkyl substituted with 1 or 2 OH, C_1-C_3 alkyl-O-(C_1-C_3 alkylenyl), 5- or 6-membered heteroaryl-C(=O), and (C_1-C_6 alkyl)-$S(O)_2$; or R^7 and R^{7a} may be taken together with the nitrogen atom to which they are both bonded to form (i) a 3- to 6-membered heterocycloalkyl, optionally substituted with a CH_3 or oxo (i.e., =O), containing the nitrogen atom, 0 or 1 O or S atoms, and carbon atoms or (ii) a 5- or 6-membered heteroaryl containing the nitrogen atom, 0 or 1 additional N atom, and carbon atoms;

wherein each substituent on a carbon atom may further be independently selected from:

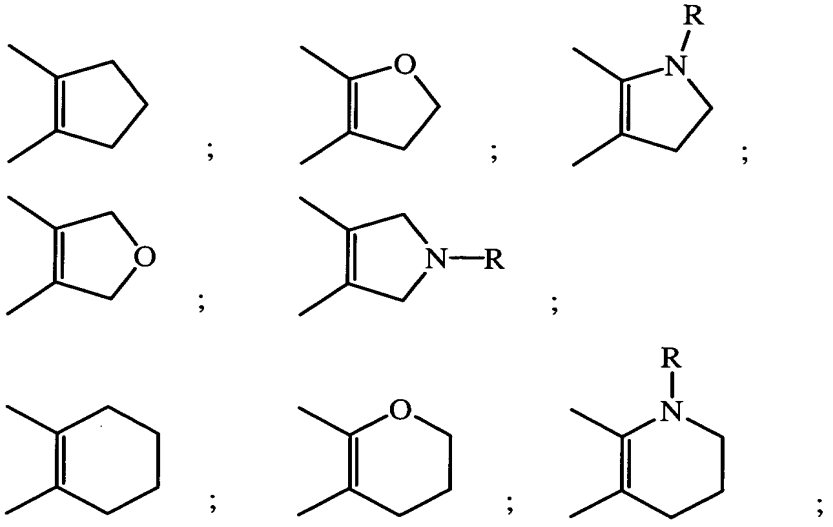
Halo;

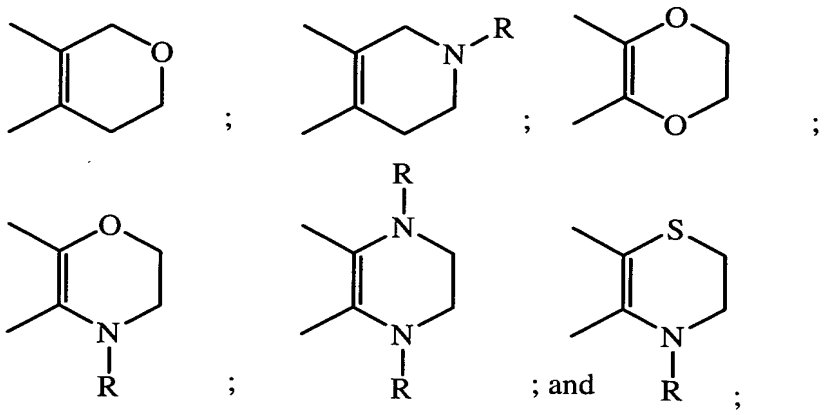
HO_2C; and

OCH_2O, wherein each O is bonded to adjacent carbon atoms to form a 5-membered ring;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





R is H or C_1-C_6 alkyl;

m is an integer of 0 or 1;

wherein each 5-membered heteroarylenyl independently is a 5-membered ring containing carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 NH, 1 N(C_1-C_6 alkyl), and 4 N, wherein the O and S atoms are not both present, and wherein the heteroarylenyl may optionally be unsubstituted or substituted with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl;

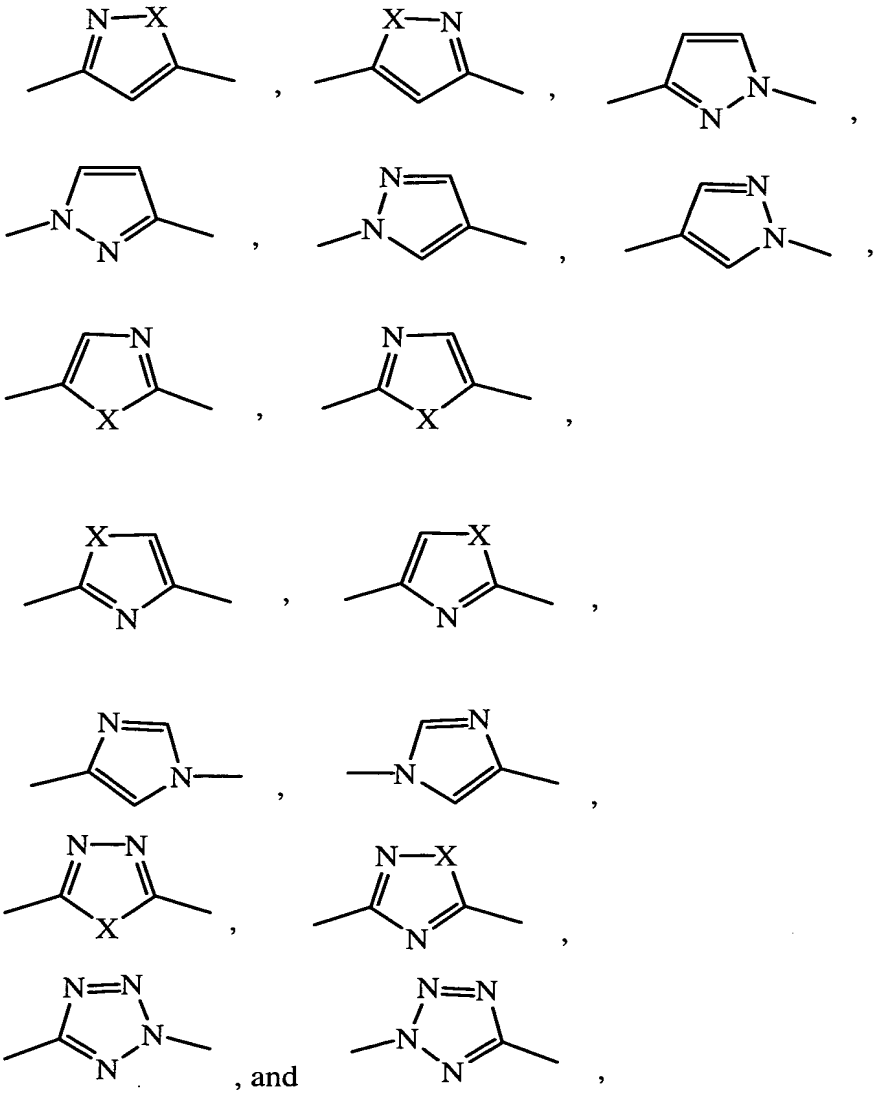
wherein each heterocycloalkyl is a ring that contains carbon atoms and 1 or 2 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 2 N(H), and 2 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings; and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any $(C_1\text{-}C_6$ alkyl$)_2$-N group, the $C_1\text{-}C_6$ alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

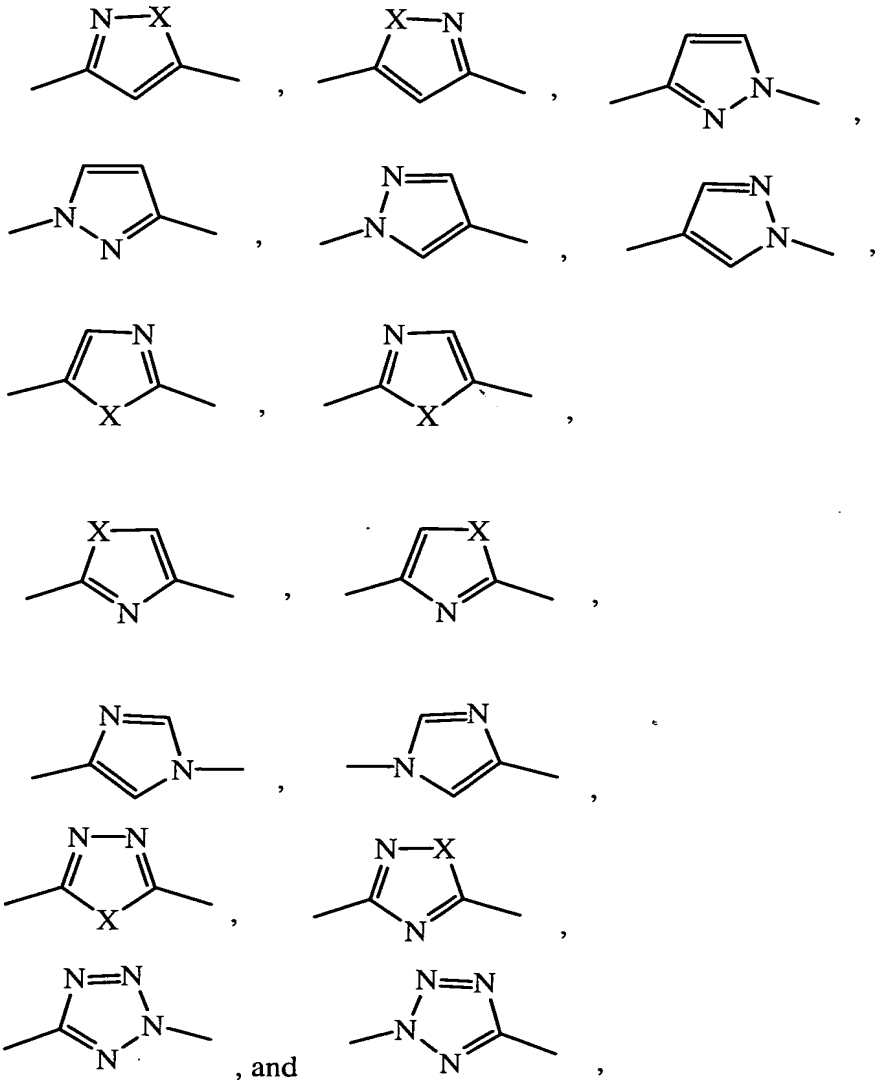
Another aspect of this invention is the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, wherein S, T, U, and W are each CH or one of S, T, U, and W is N and the other three of S, T, U, and W are each CH, and V is selected from the groups:



wherein X is O, S, or N(H).

Another aspect of this invention is the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, wherein S, T, U, and W are each CH or one of S, T, U, and W is N and the other three of S, T, U, and W are each CH, and Q is C≡C or $N(R^6)C(O)$.

Another aspect of this invention is the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, wherein S, T, U, and W are each CH or one of S, T, U, and W is N and the other three of S, T, U, and W are each CH, and Q is selected from:



wherein X is O, S, or N(H).

Another aspect of this invention is the compound of Formula Ia, or a pharmaceutically acceptable salt thereof, wherein S, T, U, and W are each CH or one of S, T, U, and W is N and the other three of S, T, U, and W are each CH, and each of R^1 and R^2 are independently selected from:

Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl);

Phenyl-(C_1-C_6 alkylenyl);

Substituted phenyl-(C_1-C_6 alkylenyl);

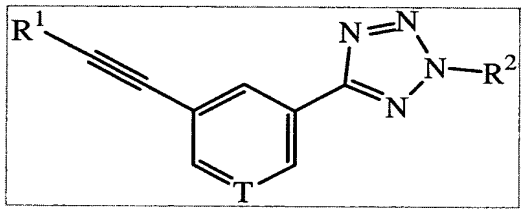
5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

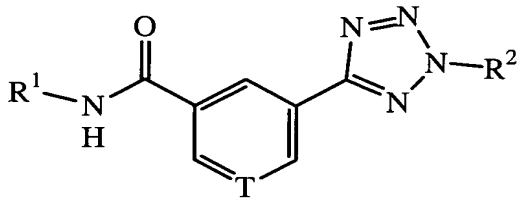
wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

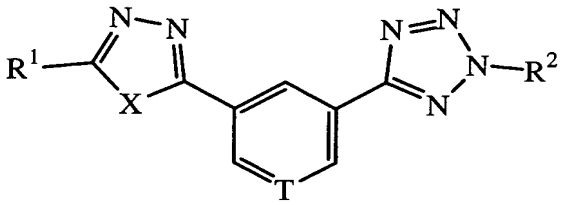
Another aspect of this invention is the compound of Formula Ia of Formulas IIa, III, IV, V, VI, VII, or VIII



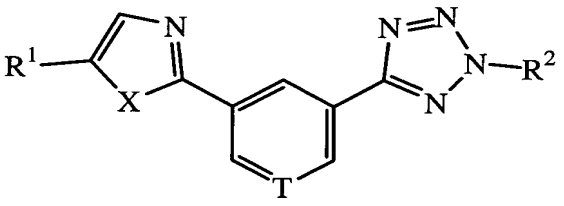
IIa



III



IV



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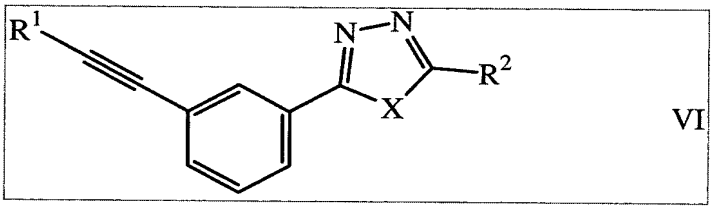
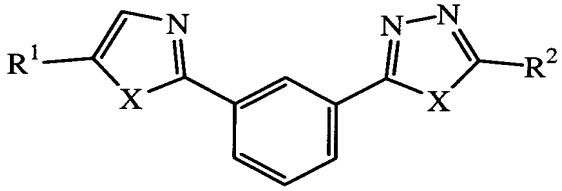
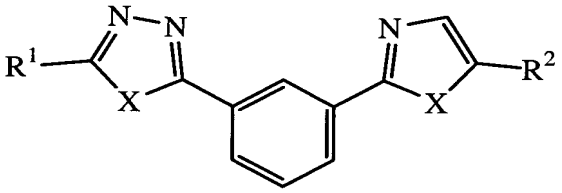


VI



VII



VIII

or a pharmaceutically acceptable salt thereof,

wherein T is CH or N, X is O, S, or N(H), and and each of R^1 and R^2 are independently selected from:

Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl);

Phenyl-(C_1-C_6 alkylenyl);

Substituted phenyl-(C_1-C_6 alkylenyl);

5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl); and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C_1-C_6 alkylenyl);

wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings, respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

wherein each group and each substituent is independently selected.

Another aspect of this invention is a compound of Formula Ia selected from:

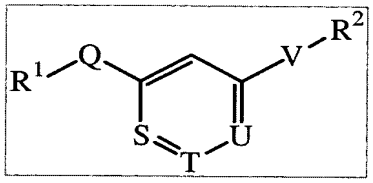
4-(5-{3-[5-(4-Chloro-phenyl)-thiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid (B5); and

4-(5-{3-[5-(4-Chloro-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid; or

a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides compounds defined by Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein R^1, Q, S, T, U, V, and R^2 are as defined above.

The invention also provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, as defined above, together with a pharmaceutically acceptable carrier, diluent, or excipient.

The invention also provides methods of inhibiting an MMP-13 enzyme in an animal, comprising administering to the animal a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The invention also provides methods of treating a disease mediated by an MMP-13 enzyme in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof, either alone or in a pharmaceutical composition.

The invention also provides methods of treating diseases such as heart disease, multiple sclerosis, osteo- and rheumatoid arthritis, arthritis other than osteo- or rheumatoid arthritis, cardiac insufficiency, inflammatory bowel disease, heart failure, age-related macular degeneration, chronic obstructive pulmonary disease, asthma, periodontal diseases, psoriasis, atherosclerosis, and osteoporosis in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof, either alone or in a pharmaceutical composition.

The invention also provides combinations, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, together with another pharmaceutically active component as described.

As seen above, the groups of Formula I include "C_1-C_6 alkyl" groups. C_1-C_6 alkyl groups are straight and branched carbon chains having from 1 to 6 carbon atoms. Examples of C_1-C_6 alkyl groups include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, and 1-hexyl.

The phrase "substituted C_1-C_6 alkyl" means a C_1-C_6 alkyl group as defined above that is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_1-C_6 alkyl groups include CH_2OH, CF_2OH, $CH_2C(CH_3)_2CO_2CH_3$, CF_3, $C(O)CF_3$, $C(O)$-CH_3, $(CH_2)_4$-S-CH_3, $CH(CO_2H)CH_2CH_2C(O)NMe_2$, $(CH_2)_5NH$-$C(O)$-NH_2, CH_2-CH_2-C(H)-(4-fluorophenyl), $CH(OCH_3)CH_2CH_3$, $CH_2SO_2NH_2$, and $CH(CH_3)CH_2CH_2OC(O)CH_3$.

The term "C_2-C_6 alkenyl" means a straight or branched, unsubstituted hydrocarbon group having from 2 to 6 carbon atoms and 1 or 2 carbon-carbon double bonds, and include allenyl groups. Typical examples of C_2-C_6 alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-3-yl, 2-penten-2-yl, and 1-hexen-6-yl.

The phrase "substituted C_2-C_6 alkenyl" means a C_2-C_6 alkenyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_2-C_6 alkenyl groups include $C(H)=C(H)CH_2OH$, $CH=CF_2$, $CH_2C(H)=C(H)-(CH_2)_2CF_2OH$, $CH_2C(=CH_2)CO_2CH_3$, $C(H)=C(H)-CF_3$, $CH_2-CH_2-C(H)=C(H)-C(O)-CH_3$, $C(H)=C(CH_3)-S-CH_3$, $C(H)=C(H)-C(H)=C(CH_3)-CO_2Me$, and $C(H)=C=C(H)OC(O)CH_3$.

The term "C_2-C_6 alkynyl" means a straight or branched, unsubstituted hydrocarbon group having from 2 to 6 carbon atoms and 1 or 2 carbon-carbon triple bonds. Typical examples of C_2-C_6 alkynyl groups include ethenyl, 1-propyn-1-yl, 1-propyn-3-yl, 1-butyn-3-yl, 2-pentyn-1-yl, and 1-hexyn-6-yl.

The phrase "substituted C_2-C_6 alkynyl" means a C_2-C_6 alkynyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_2-C_6 alkynyl groups include $C{\equiv}CCH_2OH$, $C{\equiv}CF$, $CH_2C{\equiv}C-(CH_2)_2CF_2OH$, $C{\equiv}C-CH_2CO_2CH_3$, $CH_2C{\equiv}C-CF_3$, $CH_2-CH_2-C{\equiv}C-C(O)-CH_3$, $C{\equiv}C-S-CH_3$, and $C{\equiv}C-C(O)OC(O)CH_3$.

The term "C_3-C_6 cycloalkyl" means an unsubstituted cyclic hydrocarbon group having from 3 to 6 carbon atoms. C_3-C_6 cycloalkyl may optionally contain one carbon-carbon double bond. The group C_3-C_6 cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclopenten-1-yl, cyclopenten-4-yl, and cyclohexyl.

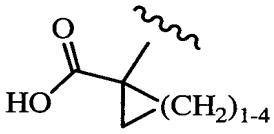
The phrase "substituted C_3-C_6 cycloalkyl" means a C_3-C_6 cycloalkyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_3-C_6 cycloalkyl

groups include 1-hydroxy-cyclopropyl, cyclobutanon-3-yl, 3-(3-phenyl-ureido)-cyclopent-1-yl, and 4-carboxy-cyclohexyl.

The phrase "3- to 6-membered heterocycloalkyl" means an unsubstituted saturated cyclic group having carbon atoms and 1 or 2 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 2 N(H), and 2 N(C_1-C_6 alkyl), wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other. Optionally, a 3- to 6-membered heterocycloalkyl may contain one carbon-carbon or carbon-nitrogen double bond. Illustrative examples of 3- to 6-membered heterocycloalkyl includes aziridin-1-yl, 1-oxa-cyclobutan-2-yl, tetrahyrdofuran-3-yl, morpholin-4-yl, 2-thiacyclohex-1-yl, 2-oxo-2-thiacyclohe-1-yl, 2,2-dioxo-2-thiacyclohex-1-yl, and 4-methyl-piperazin-2-yl.

The phrase "substituted 3- to 6-membered heterocycloalkyl" means a 3- to 6-membered heterocycloalkyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted 3- to 6-membered heterocycloalkyl include 2-hydroxy-aziridin-1-yl, 3-oxo-1-oxacyclobutan-2-yl, 2,2-dimethyl-tetrahydrofuran-3-yl, 3-carboxy-morpholin-4-yl, and 1-cyclopropyl-4-methyl-piperazin-2-yl.

The term "HO-C(=O)-(C_3-C_6 cycloalkylen-1-yl)" means a radical group of formula (A)



(A)

The term "C_1-C_6 alkylenyl" means a saturated hydrocarbon diradical that is straight or branched and has from 1 to 6 carbon atoms. C_1-C_6 alkylenyl having from 2 to 6 carbon atoms may optionally contain one carbon-carbon double bond. Illustrative examples of C_1-C_6 alkylenyl include CH_2, CH_2CH_2, $C(CH_3)H$, $C(H)(CH_3)CH_2CH_2$, and $CH_2C(H)=C(H)CH_2$. Analogously, C_1-C_3 alkylenyl means a saturated hydrocarbon diradical that is straight or branched and has from 1 to 3 carbon atoms.

The phrase "C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl)" means a C_3-C_6 cycloalkyl, as defined above, bonded through a C_1-C_6 alkylenyl, as defined above.

The phrase "Substituted C_3-C_6 cycloalkyl-(C_1-C_6 alkylenyl)-(C_1-C_6 alkylenyl)" means a substituted C_3-C_6 cycloalkyl, as defined above, bonded through a C_1-C_6 alkylenyl, as defined above.

The phrase "3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl)" means a 3- to 6-membered heterocycloalkyl, as defined above, bonded through a C_1-C_6 alkylenyl, as defined above.

The phrase "Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl)" means a substituted 3- to 6-membered heterocycloalkyl, as defined above, bonded through a C_1-C_6 alkylenyl, as defined above.

The phrase "Phenyl-(C_1-C_6 alkylenyl)" means a phenyl group bonded through a C_1-C_6 alkylenyl diradical, wherein C_1-C_6 alkylenyl is as defined above. Illustrative examples of phenyl-(C_1-C_6 alkylenyl) include benzyl, 2-phenylethyl, 1-phenyl-prop-1-yl, and 3-phenyl-pentyl.

The phrase "Substituted phenyl-(C_1-C_6 alkylenyl)" means a phenyl-(C_1-C_6 alkylenyl) as defined above, which is substituted on phenyl and/or C_1-C_6 alkylenyl with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted phenyl-(C_1-C_6 alkylenyl) include 4-fluoro-phenylmethyl, 2-(4-carboxy-phenyl)-ethyl, 1-(2,4-dimethoxy-phenyl)-2-oxo-propyl, and 1-phenyl-5,5-difluoropentyl.

The term "naphthyl" includes 1-naphthyl and 2-napthyl.

The phrase "Naphthyl-(C_1-C_6 alkylenyl)" means a naphthyl group as defined above bonded through a C_1-C_6 alkylenyl diradical, wherein C_1-C_6 alkylenyl is as defined above. Illustrative examples of naphthyl-(C_1-C_6 alkylenyl) include naphth-1-ylmethyl, 2-(naphth-1-yl)ethyl, and 3-(naphth-2-yl)-l-pentyl.

The phrase "Substituted naphthyl-(C_1-C_6 alkylenyl)" means a naphthyl-(C_1-C_6 alkylenyl) as defined above, which is substituted on naphthyl and/or C_1-C_6 alkylenyl with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted phenyl-(C_1-C_6 alkylenyl) include 4-fluoro-(naphth-1-yl)methyl, 2-(4-carboxy-(naphth-1-yl))-ethyl, 1-(2,4-dimethoxy-(naphth-1-yl))-2-oxo-propyl, and 1-(naphth-2-yl)-5,5-difluoropentyl.

The phrase "5-, 6-, 9-, and 10-membered heteroaryl" means a 5-membered, monocyclic heteroaryl, a 6-membered, monocyclic heteroaryl, a 9-membered, 6,5-fused bicyclic heteroaryl, or a 10-membered, 6,6-fused bicyclic

heteroaryl, having carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, wherein at least one of the 2 fused rings is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other, which are as defined below:

(i) The phrase "5-membered, monocyclic heteroaryl" means a 5-membered, monocyclic, aromatic ring group as defined above having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N. Illustrative examples of a 5-membered, monocyclic heteroaryl include thiophen-2-yl, furan-2-yl, pyrrol-3-yl, pyrrol-1-yl, imidazol-4-yl, isoxazol-3-yl, oxazol-2-yl, thiazol-4-yl, tetrazol-1-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-triazol-1-yl, and pyrazol-3-yl;

(ii) The phrase "6-membered, monocyclic heteroaryl" means a 6-membered, monocyclic, aromatic ring group as defined above having carbon atoms and 1 or 2 N. Illustrative examples of a 6-membered, monocyclic heteroaryl include pyridin-2-yl, pyridin-4-yl, pyrimidin-2-yl, pyridazin-4-yl, and pyrazin-2-yl;

(iii) The phrase "9-membered, 6,5-fused bicyclic heteroaryl" means a 9-membered aromatic, fused-bicyclic ring group as defined above having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N. Illustrative examples of a 9-membered, fused-bicyclic heteroaryl include indol-2-yl, indol-6-yl, iso-indol-2-yl, benzimidazol-2-yl, benzimidazol-1-yl, benztriazol-1-yl, benztriazol-5-yl, benzoxazol-2-yl, benzothiophen-5-yl, benzofuran-3-yl, and indan-1-yl; and

(iv) The phrase "10-membered, 6,5-fused bicyclic heteroaryl" means a 10-membered aromatic, fused-bicyclic ring group as defined above having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N. Illustrative examples of a 10-membered, fused-bicyclic heteroaryl include quinolin-2-yl, isoquinolin-7-yl, and benzopyrimidin-2-yl.

The phrase "substituted 5-, 6-, 9-, and 10-membered heteroaryl" means a 5-, 6-, 9-, and 10-membered heteroaryl as defined above, which is substituted on a carbon (CH) atom and/or nitrogen [N(H)] atom in the case of 5-, 9-, and 10-

membered heteroaryl, with from 1 to 4 substituents independently selected from the list above.

Illustrative examples of substituted 5-membered, monocyclic heteroaryl groups include 2-hydroxy-oxoazol-4-yl, 5-chloro-thiophen-2-yl, 1-methylimidazol-5-yl, 1-propyl-pyrrol-2-yl, 1-acetyl-pyrazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, and 2-hexyl-tetrazol-5-yl.

Illustrative examples of substituted 6-membered, monocyclic heteroaryl groups include 4-acetyl-pyridin-2-yl, 3-fluoro-pyridin-4-yl, 5-carboxy-pyrimidin-2-yl, 6-tertiary butyl-pyridazin-4-yl, 5-hdyroxymethyl-pyrazin-2-yl, and 1H-pyridin-4-one-1-yl.

Illustrative examples of substituted 9-membered, fused-bicyclic heteroaryl include 3-(2-aminomethyl)-indol-2-yl, 2-carboxy-indol-6-yl, 1-(methanesulfonyl)-iso-indol-2-yl, 5-trifluorometyl-6,7-difluoro-4-hydroxymethyl-benzimidazol-2-yl, 4-(3-methylureido)-2-cyano-benzimidazol-1-yl, 1-methylbenzimidazol-6-yl, 1-acetylbenztriazol-7-yl, 1-methanesulfonyl-indol-3-yl, 1-cyano-6-aza-indol-5-yl, and 1-(2,6-dichlorophenylmethyl)-benzpyrazol-3-yl.

Illustrative examples of substituted 10-membered, fused-bicyclic heteroaryl include 5,7-dichloro-quinolin-2-yl, isoquinolin-7-yl-1-carboxylic acid ethyl ester, and 3-bromo-benzopyrimidin-2-yl.

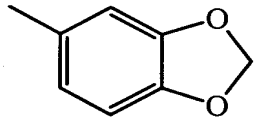
The phrase "5-membered heteroarylenyl" means a 5-membered, monocyclic, aromatic ring diradical group having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N. Optionally, heteroarylenyl may be unsubstituted or substituted on a carbon atom (CH) or nitrogen atom [N(H)] with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl Illustrative examples of a 5-membered heteroarylenyl include thiophen-2,5-diyl, furan-2,3-di-yl, pyrrol-1,3-di-yl, imidazol-1,4-diyl, tetrazol-2,5-diyl, tetrazol-1,5-dicyl, oxadiazol-3,5-diyl, thiazol-2,4-diyl, and pyrazol-1,3-diyl.

Preferred substituents for substituted phenyl, substituted naphthyl (i.e., substituted 1-naphthyl or substituted 2-naphthyl), and preferred substituents at carbon atoms for substituted 5-membered, monocyclic heteroaryl, substituted 6-membered, monocyclic heteroaryl, and substituted 9- or 10-membered, fused-

bicyclic heteroaryl are C_1-C_4 alkyl, halo, OH, O-C_1-C_4 alkyl, oxo ("=O"), 1,2-methylenedioxy, CN, NO_2, N_3, NH_2, $N(H)CH_3$, $N(CH_3)_2$, $C(O)CH_3$, $OC(O)$-C_1-C_4 alkyl, C(O)-H, CO_2H, CO_2-(C_1-C_4 alkyl), C(O)-N(H)OH, $C(O)NH_2$, C(O)NHMe, $C(O)N(Me)_2$, $NHC(O)CH_3$, $N(H)C(O)NH_2$, SH, S-C_1-C_4 alkyl, C≡CH, C(=NOH)-H, $C(=NOH)$-CH_3, CH_2OH, CH_2NH_2, $CH_2N(H)CH_3$, $CH_2N(CH_3)_2$, C(H)F-OH, CF_2-OH, $S(O)_2NH_2$, $S(O)_2N(H)CH_3$, $S(O)_2N(CH_3)_2$, S(O)-CH_3, $S(O)_2CH_3$, $S(O)_2CF_3$, or $NHS(O)_2CH_3$.

Especially preferred substituents are 1,2-methylenedioxy, methoxy, ethoxy, -O-$C(O)CH_3$, carboxy, carbomethoxy, and carboethoxy.

The term "1,2-methylenedioxy" means the diradical group -O-CH_2-O-, wherein the substituent 1,2-methylenedioxy is bonded to adjacent carbon atoms of the group which is substituted to form a 5-membered ring. Illustrative examples of groups substituted by 1,2-methylenedioxy include 1,3-benzoxazol-5-yl of formula B



B

,

which is a phenyl group substituted by 1,2-methylenedioxy.

A fused-bicyclic group is a group wherein two ring systems share two, and only two, atoms.

It should be appreciated that the groups heteroaryl or heterocycloalkyl may not contain two ring atoms bonded to each other which atoms are oxygen and/or sulfur atoms.

The term "oxo" means =O. Oxo is attached at a carbon atom unless otherwise noted. Oxo, together with the carbon atom to which it is attached forms a carbonyl group (i.e., C=O).

The term "heteroatom" includes O, S, S(O), $S(O)_2$, N, N(H), and N(C_1-C_6 alkyl).

The term "halo" includes fluoro, chloro, bromo, and iodo.

The term "amino" means NH_2.

The phrase "two adjacent, substantially sp^2 carbon atoms" means carbon atoms that comprise a carbon-carbon double bond that is capable of being substituted on each carbon atom, wherein the carbon-carbon double bond is contained in an aromatic or nonaromatic, cyclic or acyclic, or carbocyclic or heterocyclic group.

The phrase "tertiary organic amine" means a trisubstituted nitrogen group wherein the 3 substituents are independently selected from C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl, or wherein two of the substituents are taken together with the nitrogen atom to which they are bonded to form a 5- or 6-membered, monocyclic heterocycle containing one nitrogen atom and carbon atoms, and the third substituent is selected from C_1-C_{12} alkyl and benzyl, or wherein the three substituents are taken together with the nitrogen atom to which they are bonded to form a 7- to 12-membered bicyclic heterocycle containing 1 or 2 nitrogen atoms and carbon atoms, and optionally a C=N double bond when 2 nitrogen atoms are present. Illustrative examples of tertiary organic amine include triethylamine, diisopropylethylamine, benzyl diethylamino, dicyclohexylmethyl-amine, 1,8-diazabicycle[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (TED), and 1,5-diazabicycle[4.3.0]non-5-ene.

The phrase "pharmaceutical composition" means a composition suitable for administration in medical or veterinary use.

The term "admixed" and the phrase "in admixture" are synonymous and mean in a state of being in a homogeneous or heterogeneous mixture. Preferred is a homogeneous mixture.

The term "patient" means a mammal. Preferred patients are humans, cats, dogs, cows, horses, pigs, and sheep.

The term "animal" means a mammal, as defined above. Preferred animals include humans, cats, dogs, horses, pigs, sheep, cows, monkeys, rats, mice, guinea pigs, and rabbits.

The term "mammal" includes humans, companion animals such as cats and dogs, primates such as monkeys and chimpanzees, and livestock animals such as horses, cows, pigs, and sheep.

The phrase "livestock animals" as used herein refers to domesticated quadrupeds, which includes those being raised for meat and various byproducts, e.g., a bovine animal including cattle and other members of the genus Bos, a porcine animal including domestic swine and other members of the genus Sus, an ovine animal including sheep and other members of the genus Ovis, domestic goats and other members of the genus Capra; domesticated quadrupeds being raised for specialized tasks such as use as a beast of burden, e.g., an equine animal including domestic horses and other members of the family Equidae, genus Equus, or for searching and sentinel duty, e.g., a canine animal including domestic dogs and other members of the genus Canis; and domesticated quadrupeds being raised primarily for recreational purposes, e.g., members of Equus and Canis, as well as a feline animal including domestic cats and other members of the family Felidae, genus Felis.

The phrase "anticancer effective amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, or a tautomer thereof, sufficient to inhibit, halt, or cause regression of the cancer being treated in a particular patient or patient population. For example in humans or other mammals, an anticancer effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular cancer and patient being treated.

The phrase "anti-arthritic effective amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, or a tautomer thereof, sufficient to inhibit, halt, or cause regression of the arthritis being treated in a particular patient or patient population. For example in humans or other mammals, an anti-arthritic effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular arthritis and patient being treated.

The phrase "MMP-13 inhibiting amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, or a tautomer thereof, sufficient to inhibit an enzyme matrix metalloproteinase-13, including a truncated form thereof, including a catalytic domain thereof, in a particular animal or animal

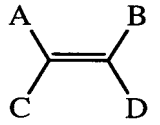
population. For example in a human or other mammal, an MMP-13 inhibiting amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular MMP-13 enzyme and patient being treated.

It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration, is within the level of ordinary skill in the pharmaceutical and medical arts, and is described below.

The phrases "effective amount" and "therapeutically effective amount" are synonymous and mean an amount of a compound of the present invention, a pharmaceutically acceptable salt thereof, or a solvate thereof, sufficient to effect an improvement of the condition being treated when administered to a patient suffering from a disease that is mediated by MMP-13 and optionally from 0 to 12 additional MMP enzymes.

The term "tautomer" means a form of invention compound existing in a state of equilibrium with an isomeric form of the invention compound, wherein the invention compound is able to react according to either form by virtue of the ability of the forms to interconvert by isomerization in situ, including in a reaction mixture, in an in vitro biological assay, or in vivo.

The term "(*E*)" means entgegen, and designates that the conformation about the double bond to which the term refers is the conformation having the two higher-ranking substituent groups, as determined according to the Cahn-Ingold-Prelog ranking system, on opposite sides of the double bond. An (*E*) double bond is illustrated below by the compound of Formula (W)

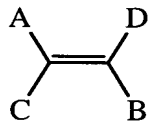


(W)

, wherein the two higher-ranking substituents are groups A and D.

The term "(*Z*)" means zusammen, and designates that the conformation about the double bond to which the term refers is the conformation having the two higher-ranking substituent groups, as determined according to the Cahn-Ingold-

Prelog ranking system, on the same side of the double bond. A (*Z*) double bond is illustrated below by the compound of Formula (X)



(X)

, wherein the two higher-ranking substituents are groups A and D.

It should be appreciated that the S1' site of MMP-13 was previously thought to be a grossly linear channel which contained an opening at the top that allowed an amino acid side chain from a substrate molecule to enter during binding, and was closed at the bottom. Applicants has discovered that the S1' site is actually composed of an S1' channel angularly connected to a newly discovered pocket which applicant calls the S1" site. The S1" site is open to solvent at the bottom, which can expose a functional group of Applicants' invention compounds to solvent. For illustrative purposes, the S1' site of the MMP-13 enzyme can now be thought of as being like a sock with a hole in the toes, wherein the S1' channel is the region from approximately the opening to the ankle, and the S1" site is the foot region below the ankle, which foot region is angularly connected to the ankle region.

More particularly, the S1' channel is a specific part of the S1' site and is formed largely by Leu218, Val219, His222 and by residues from Leu239 to Tyr244. The S1" binding site which has been newly discovered is defined by residues from Tyr246 to Pro255. The S1" site contains at least two hydrogen bond donors and aromatic groups which interact with an invention compound.

Without wishing to be bound by any particular theory, the inventors believe that the S1" site could be a recognition site for triple helix collagen, the natural substrate for MMP-13. It is possible that the conformation of the S1" site is modified only when an appropriate compound binds to MMP-13, thereby interfering with the collagen recognition process. This newly discovered pattern of binding offers the possibility of greater selectivity than what is achievable with the binding pattern of known selective inhibitors of MMP-13, wherein the known binding pattern requires ligation of the catalytic zinc atom at the active site and occupation the S1' channel, but not the S1" site.

The term "Thour245" means threonine 245 of an MMP-13 enzyme.

The term "Thour247" means threonine 247 of an MMP-13 enzyme.

The term "Met253" means methionine 253 of an MMP-13 enzyme.

The term "His251" means histidine 251 of an MMP-13 enzyme.

It should be appreciated that the matrix metalloproteinases include, but are not limited to, the following enzymes:

MMP-1, also known as interstitial collagenase, collagenase-1, or fibroblast-type collagenase;

MMP-2, also known as gelatinase A or 72 kDa Type IV collagenase;

MMP-3, also known as stromelysin or stromelysin-1;

MMP-7, also known as matrilysin or PUMP-1;

MMP-8, also known as collagenase-2, neutrophil collagenase or polymorphonuclear-type ("PMN-type") collagenase;

MMP-9, also known as gelatinase B or 92 kDa Type IV collagenase;

MMP-10, also known as stromelysin-2;

MMP-11, also known as stromelysin-3;

MMP-12, also known as metalloelastase;

MMP-13, also known as collagenase-3;

MMP-14, also known as membrane-type ("MT") 1-MMP or MT1-MMP;

MMP-15, also known as MT2-MMP;

MMP-16, also known as MT3-MMP;

MMP-17, also known as MT4-MMP;

MMP-18; and

MMP-19.

Other known MMPs include MMP-26 (Matrilysin-2).

For the purposes of this invention, the term "arthritis", which is synonymous with the phrase "arthritic condition", includes osteoarthritis, rheumatoid arthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, and psoriatic arthritis. An allosteric inhibitor of MMP-13 having an anti-arthritic effect is a compound as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the arthritic diseases and disorders listed above.

The term "IC_{50}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to inhibit an enzyme's catalytic activity by 50%.

The term "ED_{40}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to treat a disease in about 40% of a patient group.

The term "ED_{30}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to treat a disease in 30% of a patient group.

The phrase "pharmaceutical composition" means a composition suitable for administration in medical or veterinary use.

The term "admixed" and the phrase "in admixture" are synonymous and mean in a state of being in a homogeneous or heterogeneous mixture. Preferred is a homogeneous mixture.

As used herein, the phrase "cartilage damage" means a disorder of hyaline cartilage and subchondral bone characterized by hypertrophy of tissues in and around the involved joints, which may or may not be accompanied by deterioration of hyaline cartilage surface.

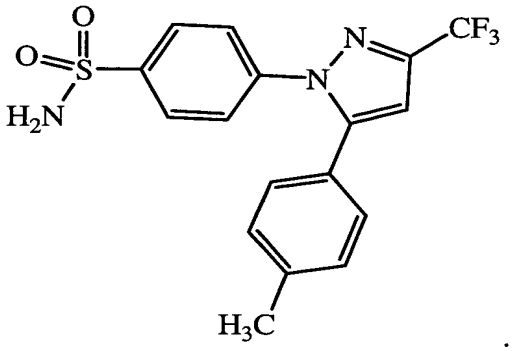
The phrase "treating", which is related to the terms "treat" and "treated", means administration of an invention combination as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the diseases and disorders listed above.

The phrase "invention compound" means a compound of Formula I, or a pharmaceutically acceptable salt thereof, as fully defined above.

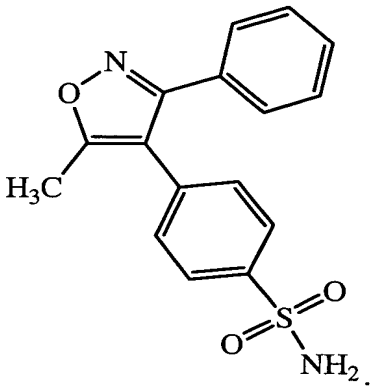
The term "nontoxic" means the efficacious dose is 10 times or greater than the dose at which a toxic effect is observed in 10% or more of a patient population.

The term "celecoxib" means the compound named 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-benzenesulfonamide. Celecoxib is a selective cyclooxygenase-2 ("COX-2") inhibitor currently approved by the FDA for the treatment of osteoarthritis, rheumatoid arthritis, and Polyposis-familial adenomatus. Celecoxib is marketed under the tradename "Celebrex". Celecoxib is currently in clinical trials for the treatment of bladder cancer, chemopreventative-

lung cancer, and post-operative pain, and is registered for the treatment of dysmenorrhea. Celecoxib has the structure drawn below:



The term "valdecoxib" means the compound named 4-(5-methyl-3-phenyl-4-isoxazolyl)-benzenesulfonamide. Valdecoxib is a selective COX-2 inhibitor that has been approved by the FDA for treating osteoarthritis, rheumatoid arthritis, dysmenorrhea, and general pain, and is marketed under the tradename "Bextra". Valdecoxib is in clinical trials for the treatment of migraine. Valdecoxib has the structure drawn below:



It should be appreciated that COX-2 is also known as prostaglandin synthase-2 and prostaglandin PGH_2 synthase.

A selective inhibitor of COX-2 means compounds that inhibit COX-2 selectively versus COX-1 such that a ratio of IC_{50} for a compound with COX-1 divided by a ratio of IC_{50} for the compound with COX-2 is greater than, or equal to, 5, where the ratios are determined in one or more assays. All that is required to determine whether a compound is a selective COX-2 inhibitor is to assay a compound in one of a number of well know assays in the art.

The term "NSAID" is an acronym for the phrase "nonsteroidal anti-inflammatory drug", which means any compound which inhibits cyclooxygenase-1 ("COX-1") and cyclooxygenase-2. Most NSAIDs fall within one of the following five structural classes: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and sulindac; (3) fenamic acid derivatives, such as mefenamic acid and meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, peroxicam, sudoxicam, and isoxicam. Other useful NSAIDs include aspirin, acetominophen, indomethacin, and phenylbutazone. Selective inhibitors of cyclooxygenase-2 as described above may be considered to be NSAIDs also.

The term "drugs", which is synonymous with the phrases "active components", "active compounds", and "active ingredients", includes celecoxib, or a pharmaceutically acceptable salt thereof, valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, and may further include one or two of the other therapeutic agents described above.

It should be appreciated that in the Summary of the Invention above, the term "Embodiment" refers to an aspect of this invention.The Embodiments in the Summary of the Invention are numbered for ease of referral.

The compounds of Formula I, or pharmaceutically acceptable salts thereof, or tautomers thereof, include compounds which are invention compounds. An allosteric inhibitor of MMP-13 is any compound of Formula I that binds allosterically into the S1' site of the MMP-13 enzyme, including the S1' channel, and a newly discovered S1" site, without ligating, coordinating, or binding the catalytic zinc of the MMP-13.

An invention compound that is an allosteric inhibitor of MMP-13 may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying an alkyne test compound for inhibition of MMP-13 as described below in Biological Methods 1 or 2, and for allosteric inhibition of MMP-13 by assaying the test invention compound for inhibition of MMP-13 in the presence of an inhibitor to the catalytic zinc of MMP-13 as described below in Biological Methods 3 or 4.

Further, an invention compound having an anti-inflammatory, an analgesic, anti-arthritic, or a cartilage damage inhibiting effect, or any combination of these effects, may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying the invention compound in any number of well known assays for measuring determining the invention compound's effects on cartilage damage, arthritis, inflammation, or pain. These assays include in vitro assays that utilize cartilage samples and in vivo assays in whole animals that measure cartilage degradation, inhibition of inflammation, or pain alleviation.

For example with regard to assaying cartilage damage in vitro, an amount of an invention compound or control vehicle may be administered with a cartilage damaging agent to cartilage, and the cartilage damage inhibiting effects in both tests studied by gross examination or histopathologic examination of the cartilage, or by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content. Further, in vivo assays to assay cartilage damage may be performed as follows: an amount of an invention compound or control vehicle may be administered with a cartilage damaging agent to an animal, and the effects of the invention compound being assayed on cartilage in the animal may be evaluated by gross examination or histopathologic examination of the cartilage, by observation of the effects in an acute model on functional limitations of the affected joint that result from cartilage damage, or by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content.

Several methods of identifying an invention compound with cartilage damage inhibiting properties are described below. The amount to be administered in an assay is dependent upon the particular assay employed, but in any event is not higher than the well known maximum amount of a compound that the particular assay can effectively accommodate.

Similarly, invention compounds having pain-alleviating properties may be identified using any one of a number of in vivo animal models of pain.

Still similarly, invention compounds having anti-inflammatory properties may be identified using any one of a number of in vivo animal models of

inflammation. For example, for an example of inflammation models, see United States patent number 6, 329,429, which is incorporated herein by reference.

Still similarly, invention compounds having anti-arthritic properties may be identified using any one of a number of in vivo animal models of arthritis. For example, for an example of arthritis models, see also United States patent number 6, 329,429.

Other mammalian diseases and disorders which are treatable by administration of an invention combination alone, or contained in a pharmaceutical composition as defined below, include: fever (including rheumatic fever and fever associated with influenza and other viral infections), common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic

retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders (preferably in livestock), epilepsy, convulsions, and septic shock.

Other aspects of the present invention are compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are ≥10, ≥20, ≥50, ≥100, or ≥1000 times more potent versus MMP-13 than versus at least two of any other MMP enzyme or TACE.

Still other aspects of the present invention are compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are selective inhibitors of MMP-13 versus 2, 3, 4, 5, 6, or 7 other MMP enzymes, or versus TACE and 1, 2, 3, 4, 5, 6, or 7 other MMP enzymes.

It should be appreciated that selectivity of a compound of Formula I, or a pharmaceutically acceptable salt thereof, is a multidimensional characteristic that includes the number of other MMP enzymes and TACE over which selectivity for MMP-13 inhibition is present and the degree of selectivity of inhibition of MMP-13 over another particular MMP or TACE, as measured by, for example, the IC_{50} in micromolar concentration of the compound for the inhibition of the other MMP enzyme or TACE divided by the IC_{50} in micromolar concentration of the compound for the inhibition of MMP-13.

As discussed above, one aspect of the present invention is novel compounds that are selective inhibitors of the enzyme MMP-13. A selective inhibitor of MMP-13, as used in the present invention, is a compound that is ≥5X more potent *in vitro* versus MMP-13 than versus at least one other matrix metalloproteinase enzyme such as, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, or MMP-14, or versus tumor necrosis factor alpha convertase ("TACE"). A preferred aspect of the present invention is novel compounds that are selective inhibitors of MMP-13 versus MMP-1.

The invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, which has an IC_{50} with any MMP enzyme that is less than or equal to 50 micromolar. Preferred are compounds of Formula I, or a pharmaceutically acceptable salt thereof, which have an IC_{50} with a human full-length MMP-13 ("hMMP-13FL") or a human MMP-13 catalytic domain ("hMMP-13CD") that is less than or equal to 50 micromolar. More preferred are compounds of Formula I, or a pharmaceutically acceptable salt thereof, which have an IC_{50} with a human full-length MMP-13 ("hMMP-13FL") or a human MMP-13 catalytic domain ("hMMP-13CD") that is less than or equal to 10 micromolar. Examples of biological methods useful for determining IC_{50}s for the invention compounds with an MMP are described below in Biological Methods 1 to 4. Any compound of Formula I, or a pharmaceutically acceptable salt thereof, or any form thereof as defined above, that does not have an IC_{50} with any MMP enzyme that is less than, or equal to, 10 micromolar is excluded from this invention.

Some of the invention compounds are capable of further forming nontoxic pharmaceutically acceptable salts, including, but not limited to, acid addition and/or base salts. The acid addition salts are formed from basic invention compounds, whereas the base addition salts are formed from acidic invention compounds. All of these forms are within the scope of the compounds useful in the invention.

Pharmaceutically acceptable acid addition salts of the basic invention compounds include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate,

phenylacetate, citrate, lactate, malate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," J. of Pharma. Sci., 1977;66:1).

An acid addition salt of a basic invention compound is prepared by contacting the free base form of the compound with a sufficient amount of a desired acid to produce a nontoxic salt in the conventional manner. The free base form of the compound may be regenerated by contacting the acid addition salt so formed with a base, and isolating the free base form of the compound in the conventional manner. The free base forms of compounds prepared according to a process of the present invention differ from their respective acid addition salt forms somewhat in certain physical properties such as solubility, crystal structure, hygroscopicity, and the like, but otherwise free base forms of the invention compounds and their respective acid addition salt forms are equivalent for purposes of the present invention.

A nontoxic pharmaceutically acceptable base addition salt of an acidic invention compound may be prepared by contacting the free acid form of the compound with a metal cation such as an alkali or alkaline earth metal cation, or an amine, especially an organic amine. Examples of suitable metal cations include sodium cation (Na^+), potassium cation (K^+), magnesium cation (Mg^{2+}), calcium cation (Ca^{2+}), and the like. Examples of suitable amines are N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, supra., 1977).

A base addition salt of an acidic invention compound may be prepared by contacting the free acid form of the compound with a sufficient amount of a desired base to produce the salt in the conventional manner. The free acid form of the compound may be regenerated by contacting the salt form so formed with an acid, and isolating the free acid of the compound in the conventional manner. The free acid forms of the invention compounds differ from their respective salt forms somewhat in certain physical properties such as solubility, crystal structure,

hygroscopicity, and the like, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain invention compounds can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are encompassed within the scope of the present invention.

Certain of the invention compounds possess one or more chiral centers, and each center may exist in the R or S configuration. An invention compound includes any diastereomeric, enantiomeric, or epimeric form of the compound, as well as mixtures thereof.

Additionally, certain invention compounds may exist as geometric isomers such as the entgegen (E) and zusammen (Z) isomers of 1,2-disubstituted alkenyl groups or cis and trans isomers of disubstituted cyclic groups. An invention compound includes any cis, trans, syn, anti, entgegen (E), or zusammen (Z) isomer of the compound, as well as mixtures thereof.

Certain invention compounds can exist as two or more tautomeric forms. Tautomeric forms of the invention compounds may interchange, for example, via enolization/de-enolization, 1,2-hydride, 1,3-hydride, or 1,4-hydride shifts, and the like. An invention compound includes any tautomeric form of the compound, as well as mixtures thereof.

Some compounds of the present invention have alkenyl groups, which may exist as entgegen or zusammen conformations, in which case all geometric forms thereof, both entgegen and zusammen, *cis* and *trans*, and mixtures thereof, are within the scope of the present invention.

Some compounds of the present invention have cycloalkyl groups, which may be substituted at more than one carbon atom, in which case all geometric forms thereof, both *cis* and *trans*, and mixtures thereof, are within the scope of the present invention.

The invention compounds also include isotopically-labelled compounds, which are identical to those recited above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that

can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of those described above in this invention can generally be prepared by carrying out the procedures incorporated by reference above or disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

All of the above-describe forms of an invention compound are included by the phrase "invention compound", a "compound of Formula I", a "compound of Formula I, or a pharmaceutically acceptable salt thereof", or any named species thereof, unless specifically excluded therefrom.

One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel®), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as etoricoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

This invention also relates to a method of or a pharmaceutical composition for treating inflammatory processes and diseases comprising administering a compound of this invention to a mammal, including a human, cat, livestock or dog, wherein said inflammatory processes and diseases are defined as above and said inhibitory compound is used in combination with one or more other therapeutically active agents under the following conditions:

A.) where a joint has become seriously inflamed as well as infected at the same time by bacteria, fungi, protozoa and/or virus, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal and/or antiviral therapeutic agents;

B.) where a multi-fold treatment of pain and inflammation is desired, said inhibitory compound is administered in combination with inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting essentially of:

(1) NSAIDs;

(2) H_1 -receptor antagonists;

(3) kinin-B_1 - and B_2 -receptor antagonists;

(4) prostaglandin inhibitors selected from the group consisting of PGD-, PGF- PGI_2 - and PGE-receptor antagonists;

(5) thromboxane A_2 (TXA_2-) inhibitors;

(6) 5-, 12- and 15-lipoxygenase inhibitors;

(7) leukotriene LTC_4 -, LTD_4/LTE_4 - and LTB_4 -inhibitors;

(8) PAF-receptor antagonists;

(9) gold in the form of an aurothio group together with one or more hydrophilic groups;

(10) immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine and methotrexate;

(11) anti-inflammatory glucocorticoids;

(12) penicillamine;

(13) hydroxychloroquine;

(14) anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone and benzbromarone;

C. where older mammals are being treated for disease conditions, syndromes and symptoms found in geriatric mammals, said inhibitory compound is administered in combination with one or more members independently selected from the group consisting essentially of:

(1) cognitive therapeutics to counteract memory loss and impairment;

(2) anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure and myocardial infarction, selected from the group consisting of:

a. diuretics;

b. vasodilators;

c. β-adrenergic receptor antagonists;

d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;

e. angiotensin II receptor antagonists;

f. renin inhibitors;

g. calcium channel blockers;

h. sympatholytic agents;

i. α_2-adrenergic agonists;

j. α-adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

(3) antineoplastic agents selected from:

a. antimitotic drugs selected from:

i. vinca alkaloids selected from:

[1] vinblastine and

[2] vincristine;

(4) growth hormone secretagogues;

(5) strong analgesics;

(6) local and systemic anesthetics; and

(7) H_2 -receptor antagonists, proton pump inhibitors and other gastroprotective agents.

The active ingredient of the present invention may be administered in combination with inhibitors of other mediators of inflammation, comprising one or more members selected from the group consisting essentially of the classes of such inhibitors and examples thereof which include, matrix metalloproteinase inhibitors, aggrecanase inhibitors, TACE inhibitors, leucotriene receptor antagonists, IL-1 processing and release inhibitors, ILra, H_1 -receptor antagonists; kinin-B_1 - and B_2 -receptor antagonists; prostaglandin inhibitors such as PGD-, PGF- PGI_2 - and PGE-receptor antagonists; thromboxane A_2 (TXA2-) inhibitors; 5- and 12-lipoxygenase inhibitors; leukotriene LTC_4 -, LTD_4/LTE_4 - and LTB_4 - inhibitors; PAF-receptor antagonists; gold in the form of an aurothio group together with various hydrophilic groups; immunosuppressive agents, e.g., cyclosporine, azathioprine and methotrexate; anti-inflammatory glucocorticoids; penicillamine; hydroxychloroquine; anti-gout agents, e.g., colchicine, xanthine oxidase inhibitors, e.g., allopurinol and uricosuric agents, e.g., probenecid, sulfinpyrazone and benzbromarone.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine and antimetabolites such as methotrexate.

The compounds of the present invention may also be used in combination with anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, including hypertension, myocardial ischemia including angina, congestive heart failure and myocardial infarction, selected from

vasodilators such as hydralazine, β-adrenergic receptor antagonists such as propranolol, calcium channel blockers such as nifedipine, α_2-adrenergic agonists such as clonidine, α-adrenergic receptor antagonists such as prazosin and HMG-CoA-reductase inhibitors (anti-hypercholesterolemics) such as lovastatin or atorvastatin.

The compounds of the present invention may also be administered in combination with one or more antibiotic, antifungal, antiprotozoal, antiviral or similar therapeutic agents.

The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as L-dopa, requip, mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase) and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, lasofoxifene, droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

The invention compounds may be used in combination with a COX-2 selective inhibitor, more preferably celecoxib (e.g., CELEBREX®), valdecoxib (e.g., BEXTRA®), parecoxib, lumiracoxib (e.g., PREXIGE®), or rofecoxib (e.g., VIOXX®), or with compounds such as etanercept (e.g., ENBREL®), infliximab (e.g., REMICADE®), leflunomide, (e.g., ARAVA®) or methotrexate, and the like.

The invention compounds may be used in combination with biological therapeutics useful for treating arthritic conditions, including CP-870, etanercept (a tumor necrosis factor alpha ("TNF-alpha") receptor immunoglobulin molecule; trade names ENBREL® and ENBREL ENTANERCEPT® by Immunex Corporation, Seattle, Washington), infliximab (an anti-TNF-alpha chimeric IgG 1K monoclonal antibody; tradename REMICADE® by Centocor, Inc., Malvern, Pennsylvania), methotrexate (tradename RHEUMATREX® by American Cyanamid Company, Wayne, New Jersey), and adalimumab (a human

monoclonal anti-TNF-alpha antibody; tradename HUMIRA® by Abbott Laboratories, Abbott Park, Illinois).

The present invention also relates to the formulation of a compound of the present invention alone or with one or more other therapeutic agents which are to form the intended combination, including wherein said different drugs have varying half-lives, by creating controlled-release forms of said drugs with different release times which achieves relatively uniform dosing; or, in the case of non-human patients, a medicated feed dosage form in which said drugs used in the combination are present together in admixture in the feed composition. There is further provided in accordance with the present invention co-administration in which the combination of drugs is achieved by the simultaneous administration of said drugs to be given in combination; including co-administration by means of different dosage forms and routes of administration; the use of combinations in accordance with different but regular and continuous dosing schedules whereby desired plasma levels of said drugs involved are maintained in the patient being treated, even though the individual drugs making up said combination are not being administered to said patient simultaneously.

The invention method is useful in human and veterinary medicines for treating mammals suffering from one or more of the above-listed diseases and disorders.

All that is required to practice a method of this invention is to administer a compound of Formula I, or a pharmaceutically acceptable salt thereof, in an amount that is therapeutically effective for preventing, inhibiting, or reversing the condition being treated. The invention compound can be administered directly or in a pharmaceutical composition as described below.

A therapeutically effective amount, or, simply, effective amount, of an invention compound will generally be from about 1 to about 300 mg/kg of subject body weight of the compound of Formula I, or a pharmaceutically acceptable salt thereof. Typical doses will be from about 10 to about 5000 mg/day for an adult subject of normal weight for each component of the combination. In a clinical setting, regulatory agencies such as, for example, the Food and Drug Administration ("FDA") in the U.S. may require a particular therapeutically effective amount.

In determining what constitutes a nontoxic effective amount or a therapeutically effective amount of an invention compound for treating, preventing, or reversing one or more symptoms of any one of the diseases and disorders described above that are being treated according to the invention methods, a number of factors will generally be considered by the medical practitioner or veterinarian in view of the experience of the medical practitioner or veterinarian, including the Food and Drug Administration guidelines, or guidelines from an equivalent agency, published clinical studies, the subject's (e.g., mammal's) age, sex, weight and general condition, as well as the type and extent of the disease, disorder or condition being treated, and the use of other medications, if any, by the subject. As such, the administered dose may fall within the ranges or concentrations recited above, or may vary outside them, ie, either below or above those ranges, depending upon the requirements of the individual subject, the severity of the condition being treated, and the particular therapeutic formulation being employed. Determination of a proper dose for a particular situation is within the skill of the medical or veterinary arts. Generally, treatment may be initiated using smaller dosages of the invention compound that are less than optimum for a particular subject. Thereafter, the dosage can be increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Pharmaceutical compositions, described briefly here and more fully below, of an invention combination may be produced by formulating the invention combination in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Alternatively, the invention compounds may be formulated separately.

Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose

acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations.

The compositions to be employed in the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents commonly employed to treat any of the above-listed diseases and disorders.

The percentage of the active ingredients of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a total concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredients are present, for example, up to about 95%.

Preferred routes of administration of an invention compound are oral or parenteral. However, another route of administration may be preferred depending upon the condition being treated. For exampled, topical administration or administration by injection may be preferred for treating conditions localized to the skin or a joint. Administration by transdermal patch may be preferred where, for example, it is desirable to effect sustained dosing.

It should be appreciated that the different routes of administration may require different dosages. For example, a useful intravenous ("IV") dose is between 5 and 50 mg, and a useful oral dosage is between 20 and 800 mg, of a compound of Formula I, or a pharmaceutically acceptable salt thereof. The dosage is within the dosing range used in treatment of the above-listed diseases, or as would be determined by the needs of the patient as described by the physician.

The invention compounds may be administered in any form. Preferably, administration is in unit dosage form. A unit dosage form of the invention compound to be used in this invention may also comprise other compounds useful in the therapy of diseases described above. A further description of

pharmaceutical formulations useful for administering the invention compounds and invention combinations is provided below.

The active components of the invention combinations, may be formulated together or separately and may be administered together or separately. The particular formulation and administration regimens used may be tailored to the particular patient and condition being treated by a practitioner of ordinary skill in the medical or pharmaceutical arts.

The advantages of using an invention compound in a method of the instant invention include the nontoxic nature of the compounds at and substantially above therapeutically effective doses, their ease of preparation, the fact that the compounds are well-tolerated, and the ease of topical, IV, or oral administration of the drugs.

Another important advantage is that the present invention compounds more effectively target a particular disease that is responsive to inhibition of MMP-13 with fewer undesirable side effects than similar compounds that inhibit MMP-13 that are not invention compounds. This is so because the instant invention compounds of Formula I, or a pharmaceutically acceptable salt thereof, do not directly, or indirectly via a bridging water molecule, ligate, coordinate to, or bind to the catalytic zinc cation of MMP-13, but instead bind at a different location from where natural substrate binds to MMP-13. The binding requirements of an allosteric MMP-13 binding site are unique to MMP-13, and account for the specificity of the invention compounds for inhibiting MMP-13 over any other MMP enzyme. This binding mode has not been reported in the art. Indeed, prior art inhibitors of MMP-13 bind to the catalytic zinc cations of other MMP enzymes as well as to the catalytic zinc cation of MMP-13, and are consequently significantly less selective inhibitors of MMP-13 enzyme.

The invention compounds which are invention compounds, and pharmaceutically acceptable salts thereof, are thus therapeutically superior to other inhibitors of MMP-13, or even tumor necrosis factor-alpha converting enzyme ("TACE"), because of fewer undesirable side effects from inhibition of the other MMP enzymes or TACE. For example, virtually all prior art MMP inhibitors tested clinically to date have exhibited an undesirable side effect known as muscoloskeletal syndrome ("MSS"). MSS is associated with administering an

inhibitor of multiple MMP enzymes or an inhibitor of a particular MMP enzyme such as MMP-1. MSS will be significantly reduced in type and severity by administering the invention compound instead of any prior art MMP-13 inhibitor, or a pharmaceutically acceptable salt thereof. The invention compounds are superior to similar compounds that interact with the catalytic zinc cation of the MMP-13 enzyme as discussed above, even if similar compounds show some selectivity for the MMP-13.

It is expected that nearly all, if not all, compounds of Formula I, or pharmaceutically acceptable salts thereof, are invention compounds.

This advantage of the instant compounds will also significantly increase the likelihood that agencies which regulate new drug approvals, such as the United States Food and Drug Administration, will approve the instant compounds versus a competing similar compound that does not allosterically bind to MMP-13 as discussed above even in the unlikely event that the two compounds behaved similarly in clinical trials. These regulatory agencies are increasingly aware that clinical trials, which test drug in limited population groups, do not always uncover safety problems with a drug, and thus all other things being equal, the agencies will favor the drug with the lowest odds of producing undesirable side effects.

Another important advantage is that the disease modifying properties of the invention compounds provide patients suffering from cartilage damage, arthritis, preferably osteoarthritis, inflammation and/or pain with both relief of symptoms and prevention or inhibition of the underlying disease pathology such as cartilage degradation. There is no currently approved drug for disease modification of cartilage damage, including in osteoarthritis.

Any invention compound is readily available, either commercially, or by synthetic methodology, well known to those skilled in the art of organic chemistry. For specific syntheses, see the examples below and the preparations of invention compound outlined in the Schemes below.

Intermediates for the synthesis of a compound of Formula I, or a pharmaceutically acceptable salt thereof, may be prepared by one of ordinary skill in the art of organic chemistry by adapting various synthetic procedures incorporated by reference above or that are well-known in the art of organic chemistry. These synthetic procedures may be found in the literature in, for

example, Reagents for Organic Synthesis, by Fieser and Fieser, John Wiley & Sons, Inc, New York, 2000; Comprehensive Organic Transformations, by Richard C. Larock, VCH Publishers, Inc, New York, 1989; the series Compendium of Organic Synthetic Methods,1989,by Wiley-Interscience; the text Advanced Organic Chemistry, 4th edition, by Jerry March, Wiley-Interscience, New York,1992; or the Handbook of Heterocyclic Chemistry by Alan R. Katritzky, Pergamon Press Ltd, London, 1985, to name a few. Alternatively, a skilled artisan may find methods useful for preparing the intermediates in the chemical literature by searching widely available databases such as, for example, those available from the Chemical Abstracts Service, Columbus, Ohio, or MDL Information Systems GmbH (formerly Beilstein Information Systems GmbH), Frankfurt, Germany.

Preparations of the invention compounds may use starting materials, reagents, solvents, and catalysts that may be purchased from commercial sources or they may be readily prepared by adapting procedures in the references or resources cited above. Commercial sources of starting materials, reagents, solvents, and catalysts useful in preparing invention compounds include, for example, The Aldrich Chemical Company, and other subsidiaries of Sigma-Aldrich Corporation, St. Louis, Missouri, BACHEM, BACHEM A.G., Switzerland, or Lancaster Synthesis Ltd, United Kingdom.

Syntheses of some invention compounds may utilize starting materials, intermediates, or reaction products that contain a reactive functional group. During chemical reactions, a reactive functional group may be protected from reacting by a protecting group that renders the reactive functional group substantially inert to the reaction conditions employed. A protecting group is introduced onto a starting material prior to carrying out the reaction step for which a protecting group is needed. Once the protecting group is no longer needed, the protecting group can be removed. It is well within the ordinary skill in the art to introduce protecting groups during a synthesis of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and then later remove them. Procedures for introducing and removing protecting groups are known and referenced such as, for example, in Protective Groups in Organic Synthesis, 2nd ed., Greene T.W. and

Wuts P.G., John Wiley & Sons, New York: New York, 1991, which is hereby incorporated by reference.

Thus, for example, protecting groups such as the following may be utilized to protect amino, hydroxyl, and other groups: carboxylic acyl groups such as, for example, formyl, acetyl, and trifluoroacetyl; alkoxycarbonyl groups such as, for example, ethoxycarbonyl, tert-butoxycarbonyl (BOC), β,β,β-trichloroethoxycarbonyl (TCEC), and β-iodoethoxycarbonyl; aralkyloxycarbonyl groups such as, for example, benzyloxycarbonyl (CBZ), para-methoxybenzyloxycarbonyl, and 9-fluorenylmethyloxycarbonyl (FMOC); trialkylsilyl groups such as, for example, trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBDMS); and other groups such as, for example, triphenylmethyl (trityl), tetrahydropyranyl, vinyloxycarbonyl, ortho-nitrophenylsulfenyl, diphenylphosphinyl, para-toluenesulfonyl (Ts), mesyl, trifluoromethanesulfonyl, and benzyl. Examples of procedures for removal of protecting groups include hydrogenolysis of CBZ groups using, for example, hydrogen gas at 50 psi in the presence of a hydrogenation catalyst such as 10% palladium on carbon, acidolysis of BOC groups using, for example, hydrogen chloride in dichloromethane, trifluoroacetic acid (TFA) in dichloromethane, and the like, reaction of silyl groups with fluoride ions, and reductive cleavage of TCEC groups with zinc metal.

Compounds of Formula I may be prepared according to the synthetic route outlined in Scheme 1. In Scheme 1, commercially available 3-cyanobenzoic acid **1** undergoes a 3 + 2 cycloaddition reaction with azides selected from sodium azide, tributyltin azide, or trimethylsilyl azide in a suitable solvent such as toluene or p-dioxane and in the presence of triethylamine hydrochloride or ammonium chloride to form the corresponding tetrazole derivative. The carboxylic acid functionality is reacted with HCl in methanol at room temperature or under reflux conditions to give the ester intermediate **2**. Compound **2** in Scheme 1 is allowed to react with a variety of alkyl halides or mesylates of commercially available alcohols in the presence of a base such as triethylamine, cesium carbonate, or sodium carbonate in a suitable solvent such as acetonitrile or dimethylformamide.

The resulting 1- and 2-substituted regioisomers are separated analytically pure using purification methods known in the art such as silica gel

chromatography or recrystallization from solvents such as hexane/ethyl acetate or petroleum ether/diethyl ether. The ester functionality of intermediate **3** is converted to the corresponding acid **5** in the presence of a base such as sodium or lithium hydroxide in a protic solvent such as ethanol, methanol, or water. Acidification of the carboxylate salt using an acid such as hydrochloric acid, acetic acid, or trifluoroacetic acid yields the acid intermediate **5**. The acid is converted to the acid chloride with oxalyl chloride or allowed to react with a coupling agent such as DCC or EDC in the presence of HOBT in a suitable solvent such as dichloromethane, tetrahydrofuran, or dimethylformamide. These reactive intermediates are coupled with a variety of primary and secondary amine nucleophiles including benzylamine, isopropylamine, and 3-picolylmethylamine to name a few.

Compounds of Formula I wherein S, T, or U are C-OCH3 are prepared as shown in Scheme 2. The 3-bromo-4-methoxybenzonitrile **7** is converted to the tetrazole and alkylated to compounds **9** and **10** using reaction conditions described for intermediates **2**,**3**, and **4** in Scheme 1. Intermediate **9** is carbonylated in the presence of a suitable coupling reagent such as a palladium catalyst, including bis(triphenylphosphinyl)chloride, palladium acetate, or palladium tetrakis triphenylphosphine, in the presence of a base such as a tertiary organic amine, including triethylamine or diisopropylethylamine, in a protic solvent such as methanol and under an atmosphere of carbon monoxide whose pressure and temperature may require as high as 500 psi and 100 °C. Compound **11** can then be converted to a variety of amides **13** utilizing the experimental conditions previously described in Scheme 1.

Compound **7** in Scheme 2 can be replaced with commercially available pyridine based nitriles **14** as shown in Scheme 3. These compounds are converted to the corresponding tetrazole amides **20** utilizing the reaction conditions described in Scheme 2 for compound **14**.

Alternatively in Scheme 4, the acid chloride prepared in Scheme 1 can be converted to the corresponding primary alcohol **22** in the presence of a suitable reducing agent such as lithium aluminum hydride or sodium borohydride in an aprotic solvent such a dichloromethane or tetrahydrofuran at temperatures ranging

between 0 °C and 60 °C. The alcohol **22** is converted to the corresponding bromide **23** using phosphorous tribromide in a halogenated solvent including dichloromethane, carbon tetrachloride, or chloroform. Intermediate **23** can be coupled with a variety of primary and secondary amines in the presence of a tertiary amine including diisopropylethylamine or triethylamine in suitable solvent such as dichloromethane or tetrahydrofuran at temperatures ranging from as low as room temperature to as high as reflux to give tetrazole amine **24**. Coupling alkyl halide **23** with a variety of alcohols including benzyl alcohol or phenol and in the presence of a base such as sodium hydride or cesium carbonate in an appropriate solvent such as dimethylformamide or tetrahydrofuran yields the corresponding tetrazole ether derivative **25**.

The synthesis of alkyne derivatives is presented in Scheme 5. The iodo substituted intermediate **28** is coupled with an appropriately substituted alkyne such as 3-phenyl-1-propyne or (1,1-difluoro-prop-2-ynyl)-benzene in the presence of copper(I) iodide and a tertiary organic base including diisopropylethylamine or triethylamine. The reaction is catalyzed by a palladium catalyst such as tetrakis (triphenylphosphine) palladium(0) or bis(triphenylphosphine)palladium(II) dichloride to yield the corresponding alkyne derivatives **30**.

The synthesis of compounds of Formula I wherein V is a 5-membered heteroaryleneyl such as an oxazolenyl or thiazolenyl is illustrated below in Scheme 6. In Scheme 6, 3-iodo-benzoic acid (1) is allowed to react with an alpha-amino ketone hydrochloride of formula (2) (prepared, for example, by allowing ammonia to react with an alpha-(Cl, Br, or I)-4-carboxymethyl-acetophenone in a solvent such as tetrahydrofuran ("THF") at a temperature of from about -33 to room temperature) to give the keto-amide compound of formula (3). The compound of formula (3) is cyclized under acidic dehydrating conditions such as with an acid catalyst selected from polyphosphoric acid, para-toluenesulfonic acid, amberlyst-15 resin, methanesulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, titanium tetrachloride, and the like in the presence of a suitable dehydrating reagent selected from a Dean-Stark trap, activated 3-angstrom molecular sieves, anhydrous magnesium sulfate, phosphorous pentoxide, and the like in a suitable solvent such as toluene,

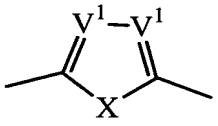
dichloromethane ("DCM"), THF, xylenes, and the like at a suitable temperature such as from about 0°C to about 200°C to give the oxazole-ester of formula (4). The oxazole-ester of formula (4) is saponified to give the corresponding oxazole-acid, which is then coupled with a 3-substituted propylene of formula (5) using conditions described above in previous examples or palladium, copper(I) iodide, and Hünig's base or 1,8-diazabicyclo[5.4.0]undec-7-ene to give an oxazole compound of formula (6).

Alternatively in Scheme 6, the keto-amide compound of formula (3) is sulfurated with, for example, P_2S_5, to give the corresponding keto-thioamide, which is cyclized as previously described for cyclization of the keto-amide of formula (3) to give the thiazole-ester of formula (7). The thiazole-ester of formula (7) is then converted in several steps to the thiazole compound of the present invention of formula (8) according to the methods described above for conversion of the oxazole-ester of formula (4) to the compound of formula (6).

Another synthesis of compounds of Formula I wherein V is a 5-membered heteroaryleneyl such as a oxadiazolenyl or thiadiazolenyl is illustrated below in Scheme 7. In Scheme 7, 3-iodo-benzoic acid (1) is coupled with N-tertbutyloxycarbonyl-hydrazine ("N-BOC-hydrazine") in the presence of a suitable coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride ("EDC," "EDCI," or "EDAC"), N,N′-carbonyldiimidazole ("CDI") or N,N′-dicyclohexylcarbodiimide ("DCC") with 1-hydroxybenzotriazole ("HOBt") in a suitable solvent such as THF, DCM, and the like at a suitable temperature such as from about -30°C to about 100°C, followed by acid catalyzed cleavage of the BOC group (e.g., HCl gas in DCM or ethyl acetate) to give an acyl-hydrazine, which is then coupled in a similar fashion with 4-carbomethoxybenzoic acid (2) to give the bisacyl-hydrazine-ester of formula (3). Following procedures analogous to those described above for Scheme 6, the bisacyl-hydrazine-ester of formula (3) is then cyclized under acid dehydrating conditions to give the oxadiaole-ester of formula (4), which is saponified, and the resulting oxadiazole-acid coupled with a 3-substituted propyne of formula (5) to give an oxadiazole compound of formula (6).

Alternatively, following procedures analogous to those described above for Scheme 6, the bisacyl-hydrazine-ester of formula (3) is sulfurated with P_2S_5 or the like, and cyclized under acid dehydrating conditions to give the oxadiaole-ester of formula (7), which is saponified, and the resulting oxadiazole-acid coupled with a 3-substituted propyne of formula (5) to give a thiadiazole compound of formula (8).

The synthesis of compounds of Formula I wherein Q is



such as an oxazolenyl or thiazolenyl is illustrated below in Schemes 8-10. In Scheme 8, 3-cyano-benzoic acid (1) is allowed to react with an alpha-amino ketone hydrochloride of formula (2) (prepared, for example, by allowing ammonia to react with an alpha-(Cl, Br, or I)-4-methoxy-acetophenone in a solvent such as tetrahydrofuran ("THF") at a temperature of from about -33 to room temperature) to give the keto-amide compound of formula (3). The compound of formula (3) is condensed with sodium azide under conventional tetrazole-ring forming conditions such as in the presence of a weak acid such as triethylamine hydrochloride in a suitable solvent such as THF and the like at temperatures from about 0°C to about 120°C to give the tetrazole-keto-amide of formula (4). Tri-(n-butyl)tin azide may be used also to synthesize the tetrazole-keto-amide of formula (4). Following the procedures described above for Scheme 6, the keto-amide of formula (4) is then cyclized under acid dehydrating conditions to give the oxazole-tetrazole of formula (5). The oxazole-tetrazole of formula (5) is alkylated with a suitable alkylating agent such as the bromo-ester of formula (6), and the resulting oxazole-tetrazole-ester is hydrolyzed under acidic conditions to give an oxazole-acid compound of formula (7).

Alternatively, following procedures analogous to those described above for Scheme 6, the keto-amide of formula (4) is sulfurated with P_2S_5 or the like, and cyclized under acid dehydrating conditions to give the thiazole-tetrazole of formula (8). The thiazole-tetrazole of formula (8) is then alkylated with a suitable alkylating agent such as the bromo-ester of formula (6), and the resulting thiazole-tetrazole-ester is hydrolyzed under acidic conditions to give a thiazole-acid compound of formula (9).

In Scheme 9, isophthalic acid monomethyl ester of formula (1) is coupled with N-BOC-hydrazine and the BOC group is cleaved as described above for Scheme 7 to give the ester-acylhydrazine hydrochloride of formula (2). The ester-acylhydrazine hydrochloride (2) is coupled with 4-carboxymethylbenzoic acid methyl ester of formula (3) using conventional conditions such as EDAC·HCl, HOBt, N,N′-dimethylformamide ("DMF"), as described above to give the ester-bisacylhydrazine of formula (4). The ester-bisacylhydrazine of formula (4) is cyclized under acidic dehydrating conditions such as those described above for Scheme 7 to give the ester-oxadiazole of formula (5). The ester-oxadiazole of formula (5) is then saponified to give the corresponding acid-oxadiazole, which is coupled with an alpha-amino ketone hydrochloride of formula (6) under conventional conditions as described above for Scheme 8 to give the keto-amide-oxadiazole-ester of formula (7). The keto-amide-oxadiazole-ester of formula (7) is cyclized under acidic dehydrating conditions as described above, and the ester saponified to give the oxazole-oxadiazole-ester of formula (8).

Alternatively, following the procedures described above for Scheme 7, the ester-bisacylhydrazine of formula (4) is sulfurated, and the intermediate is cyclized under acidic dehydrating conditions to give a compound of formula (9), which is converted to the compound of formula (10) as described above, which is converted to the compound of formula (11) as described above.

Alternatively, following the procedures described above for Scheme 6, the compound of formula (7) is sulfurated, and the intermediate is cyclized under acidic dehydrating conditions to give a compound of formula (12) as described above.

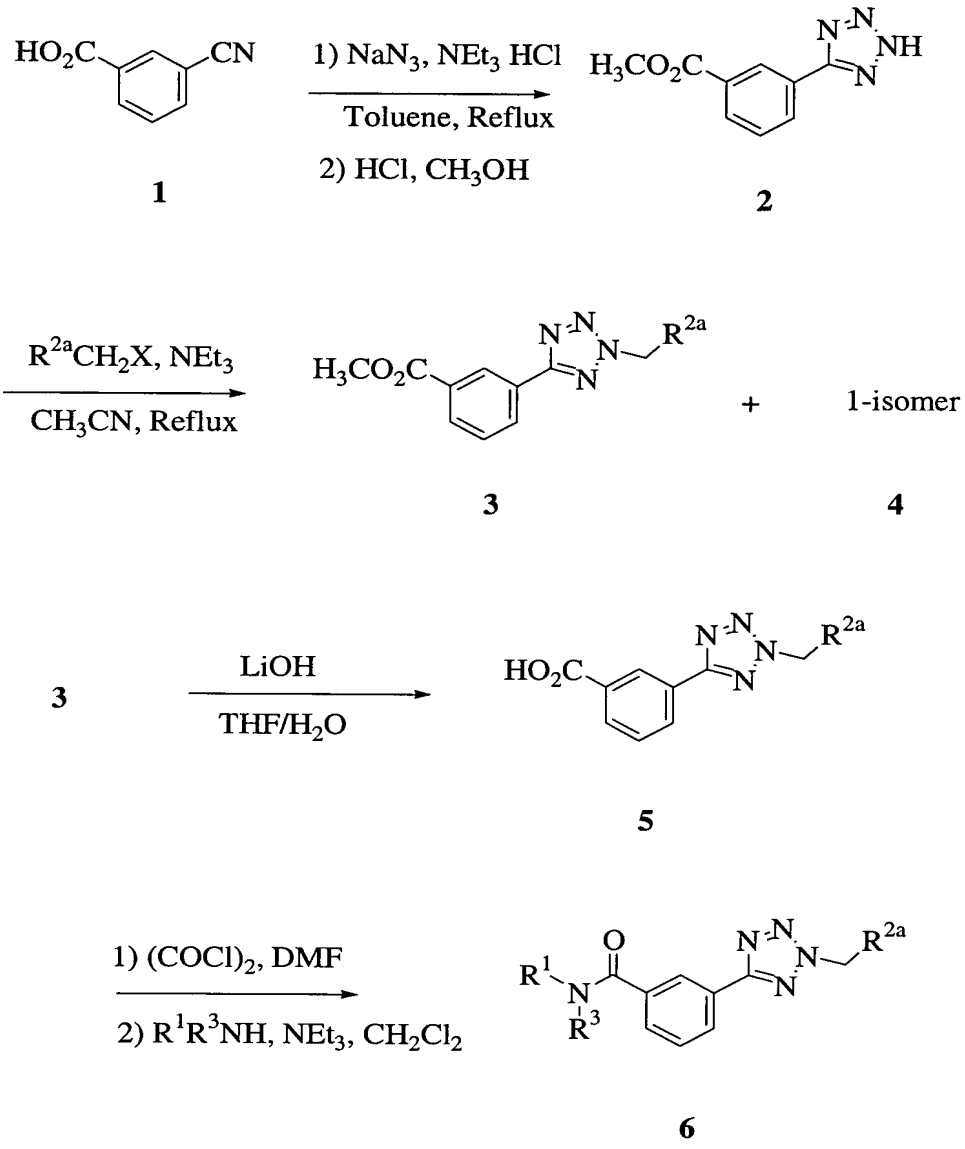
Alternatively, following the procedures described above for Schemes 6 and 7, the compound of formula (10) is sulfurated, and the intermediate is cyclized under acidic dehydrating conditions to give a compound of formula (13) as described above.

Alternatively in Scheme 9a, compounds of formulas (5) or (9) may be converted to compounds of formulas (17), (18), (19), and (20) by substituting the compound of Formula (14) in Scheme 9a for the compound of formula (6) in Scheme 9, and converting the resulting compounds as described for Scheme 9.

In Scheme 10, isophthalic acid monomethyl ester of formula (1) is coupled with 4-methoxybenzylamine of formula (2) using conventional conditions as described previously to give the keto-amide of formula (3). The ester-keto-amide of formula (3) is sturcturally related to the ester-bisacylhydrazine of formula (4) in Scheme 9. In a manner similar to that illustrated above in Scheme 9 for the conversion of the ester-bisacylhydrazine of formula (4) to the compounds of formulas (8), (11), (12), and (13), the compounds of formulas (4), (5), (6), and (7), respectively in Scheme 10 may be prepared.

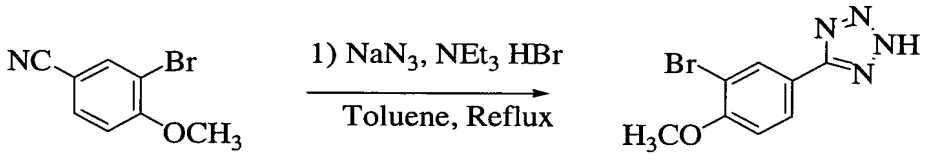
Alternatively in Scheme 10, a compound of formula (3) may be converted to compounds of formulas (8), (9), (10), and (11) by substituting 4-methoxy-benzoylhydrazine hydrochloride for the alpha-amino ketone hydrochloride of formula (6) in Scheme 9, and converting the resulting compounds as described for Scheme 9.

Scheme 1.

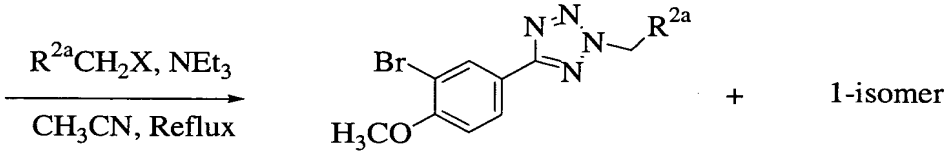


wherein R^1 and R^3 are as defined above for Formula I and $R^{2a}CH_2$ is a subset of the group R^2 of Formula I.

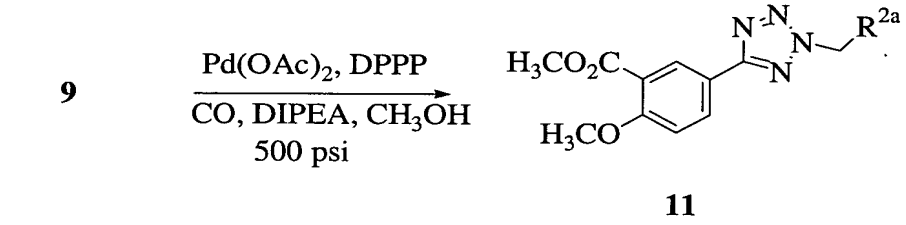
Scheme 2.



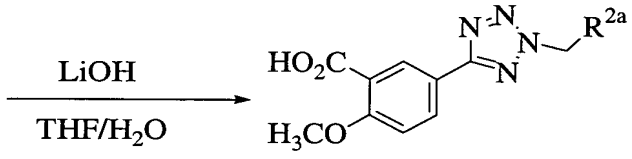
7 **8**



9 **10**



11



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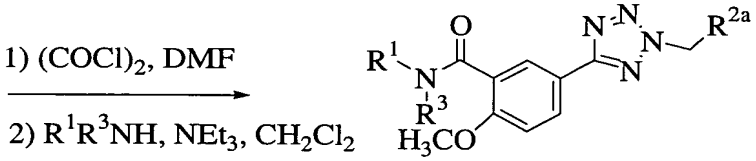
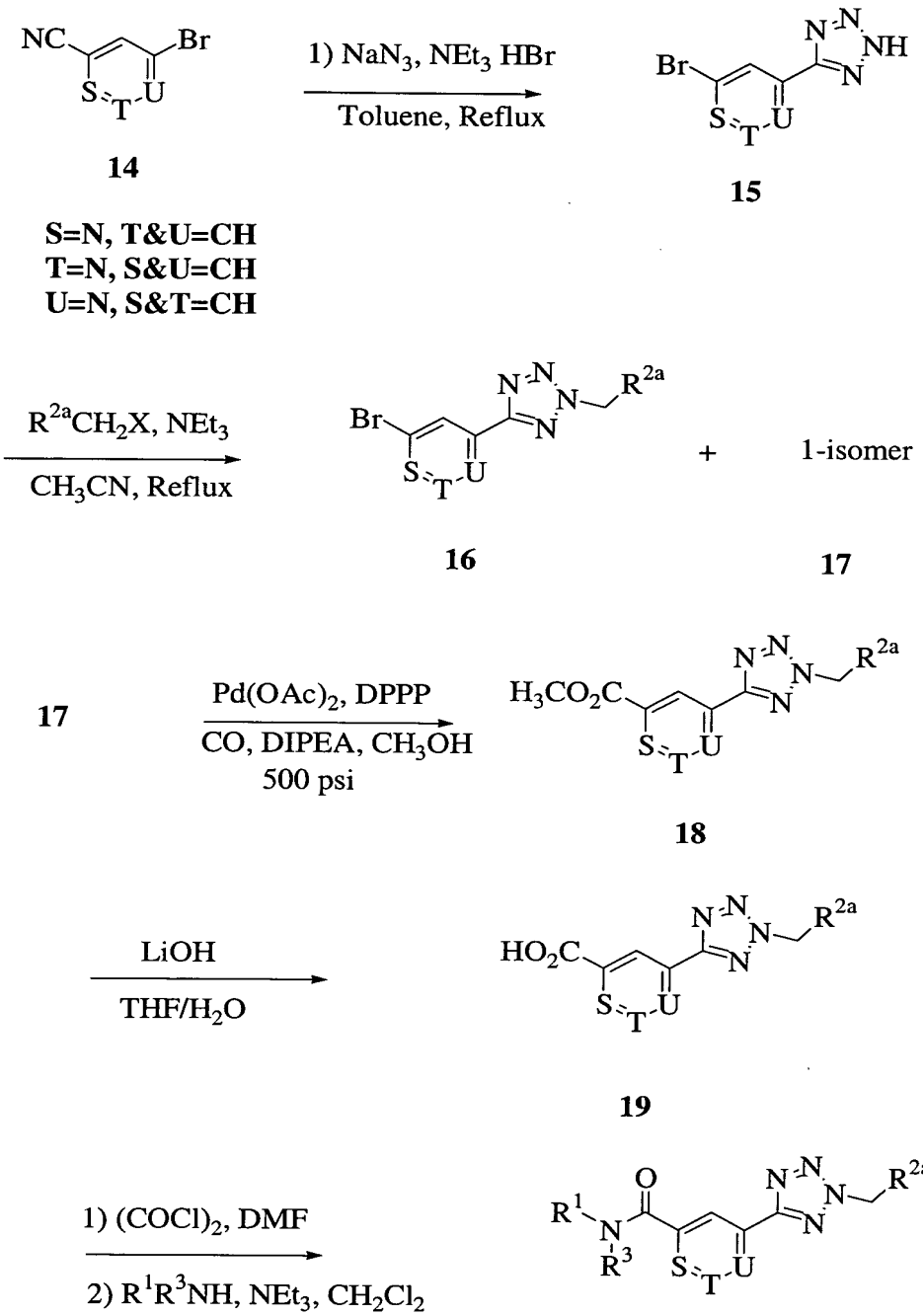


13

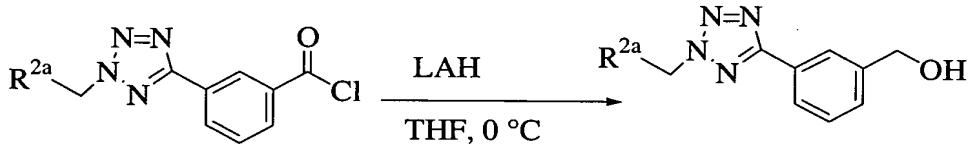
wherein R^1 and R^3 are as defined above for Formula I and $R^{2a}CH_2$ is a subset of the group R^2 of Formula I.

Scheme 3.

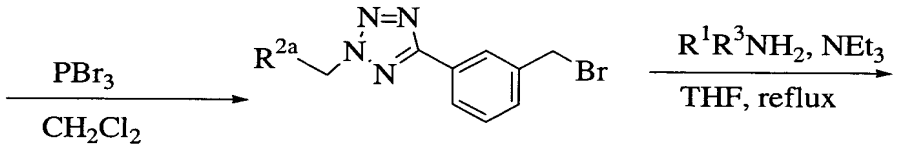


wherein R^1 and R^3 are as defined above for Formula I and $R^{2a}CH_2$ is a subset of the group R^2 of Formula I.

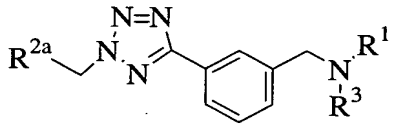
Scheme 4.



21 **22**



23



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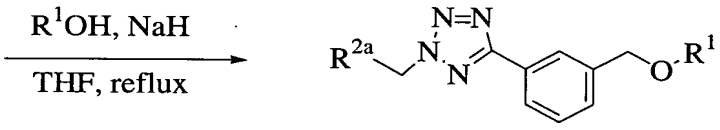
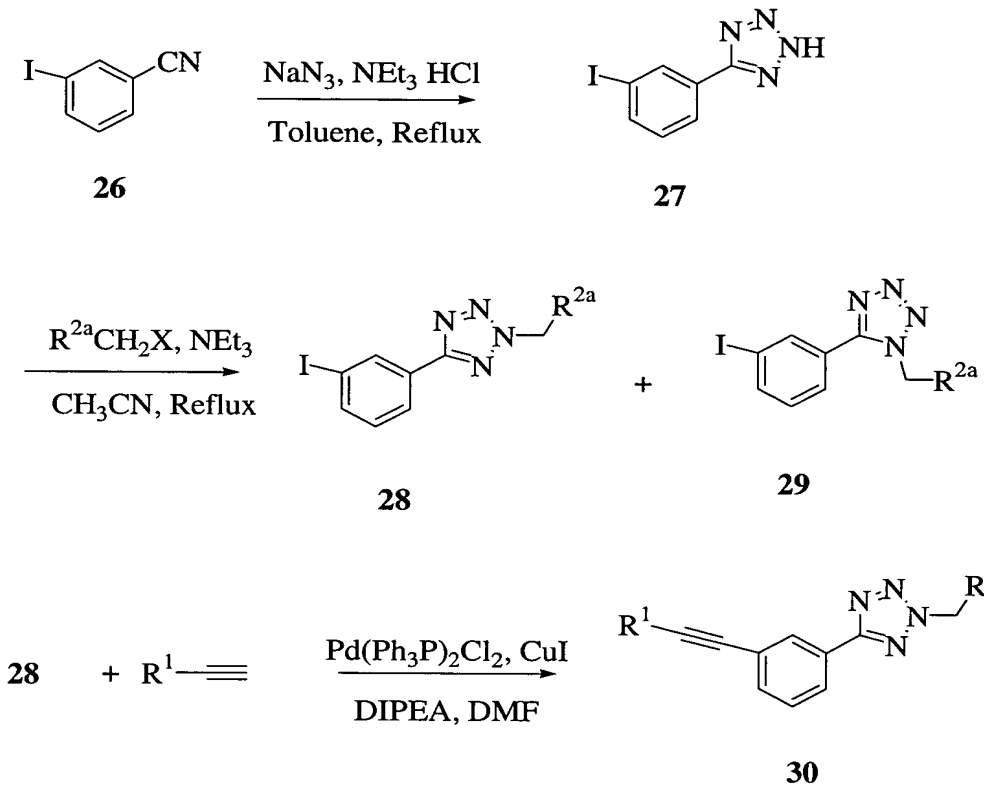


25

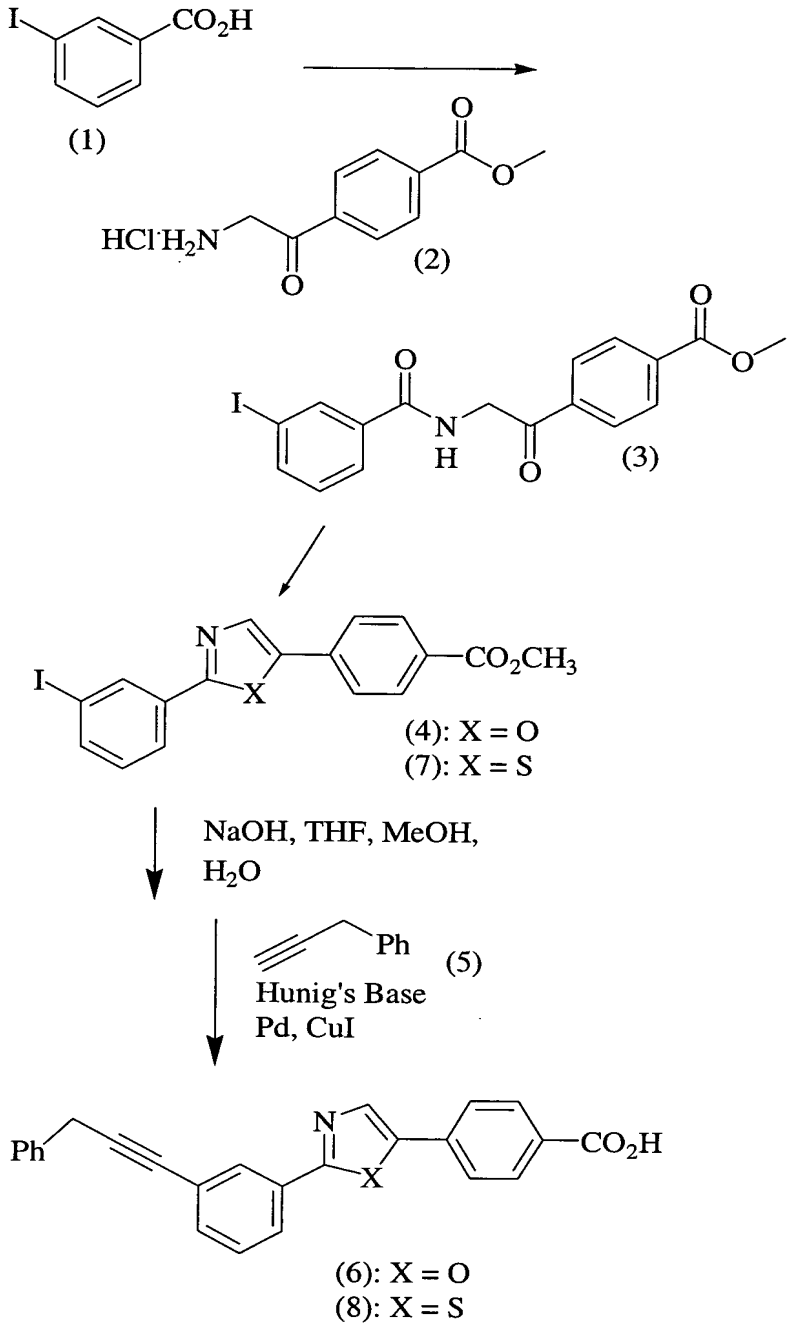
wherein R^1 and R^3 are as defined above for Formula I and $R^{2a}CH_2$ is a subset of the group R^2 of Formula I.

Scheme 5.

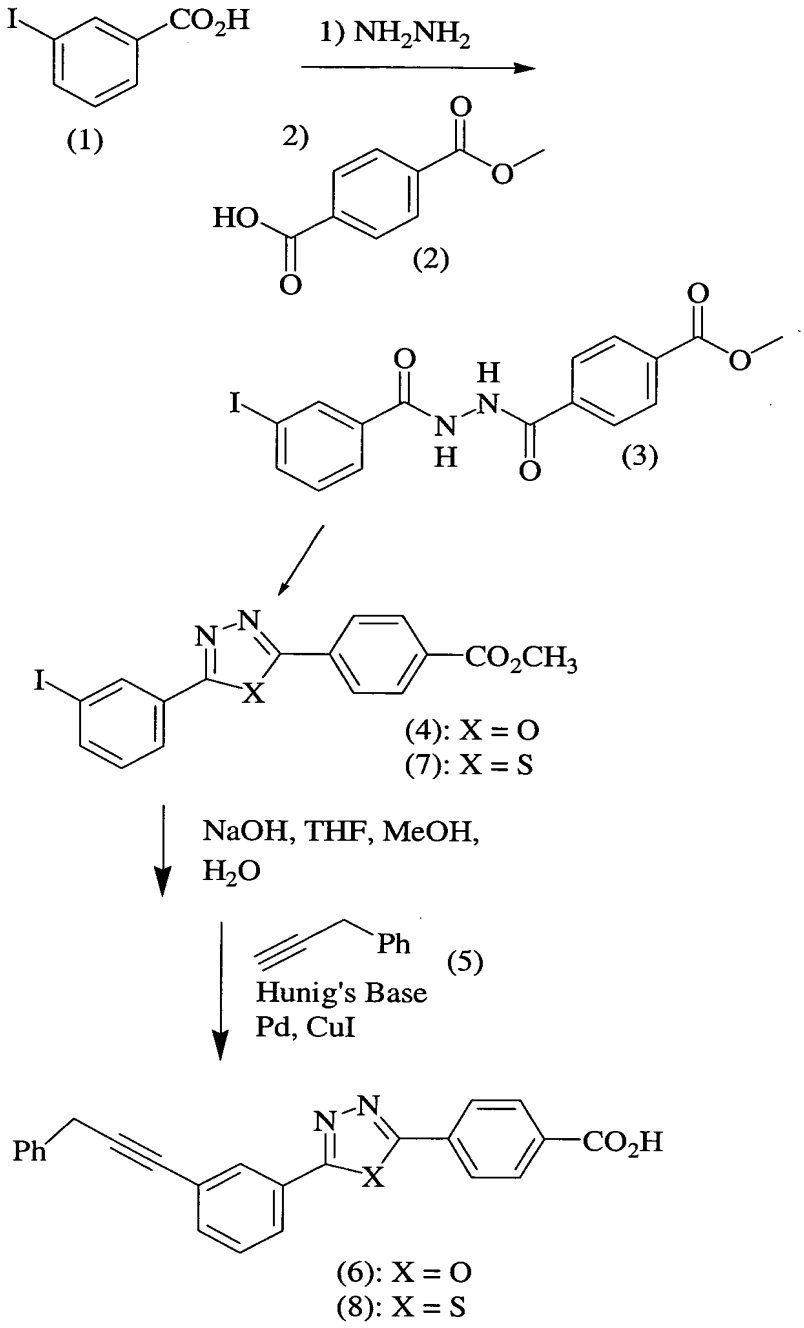


wherein R^1 and R^3 are as defined above for Formula I and $R^{2a}CH_2$ is a subset of the group R^2 of Formula I.

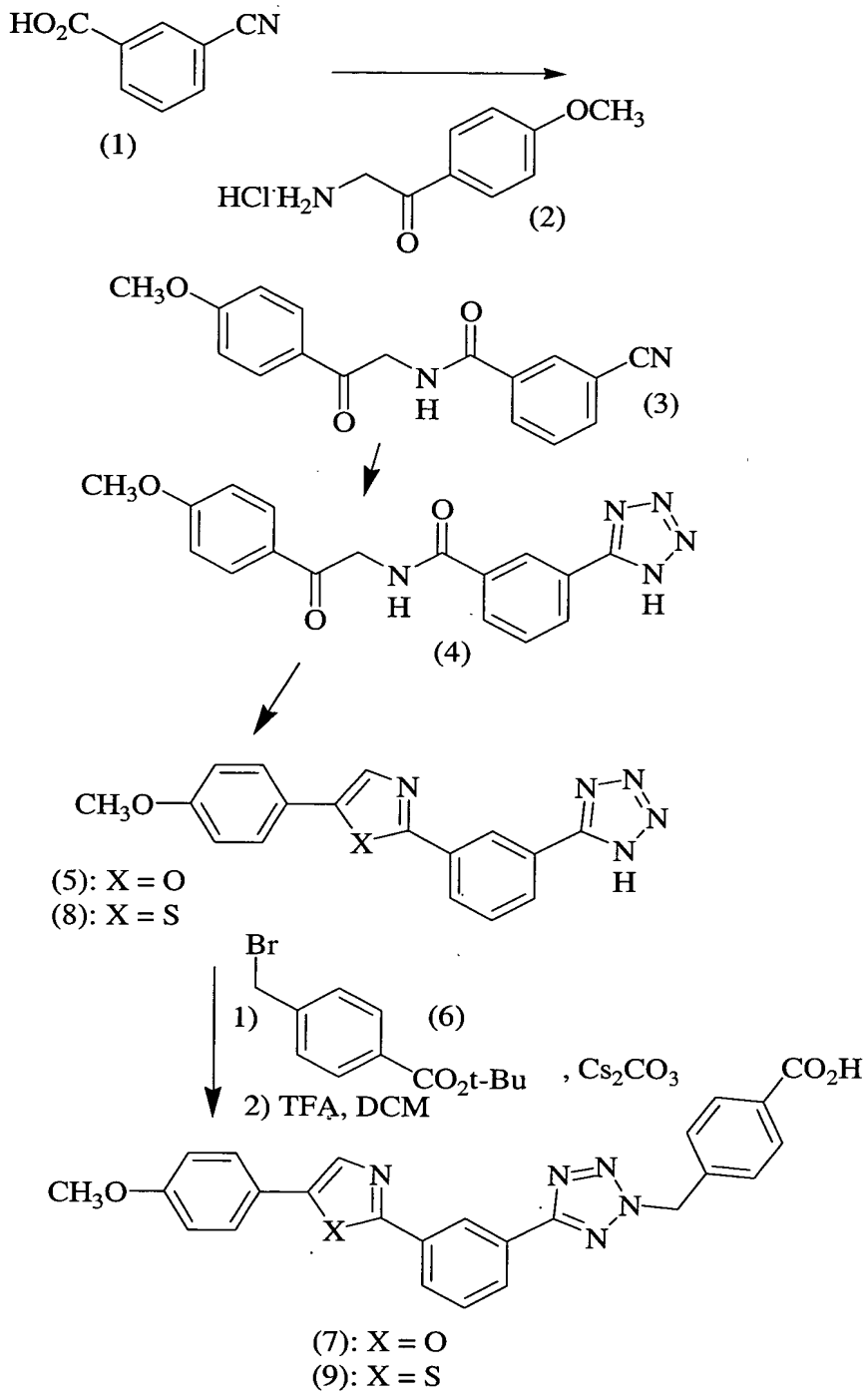
Scheme 6.


I
CO2H
(1)
HCl·H2N
O
O
O
(2)
I
N
H
O
O
O
O
(3)
N
X
I
CO2CH3
(4): X = O
(7): X = S
NaOH, THF, MeOH,
H2O
Ph
(5)
Hunig's Base
Pd, CuI
Ph
N
X
CO2H
(6): X = O
(8): X = S

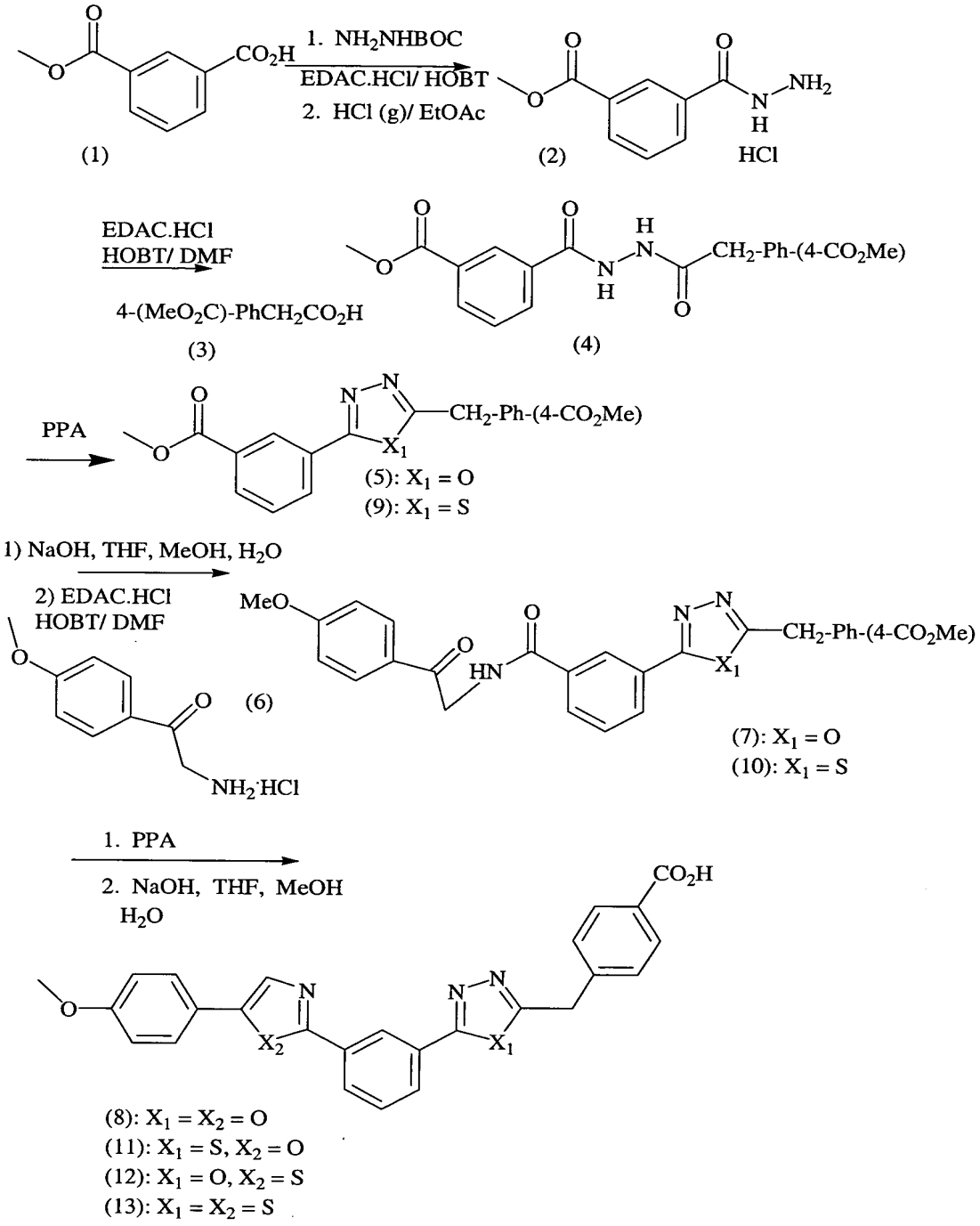
Scheme 7.


I
CO2H
(1)
1) NH2NH2
2)
HO
O
O
O
(2)
I
O
N
H
H
N
O
O
O
(3)
N
N
X
I
CO2CH3
(4): X = O
(7): X = S
NaOH, THF, MeOH,
H2O
Ph
(5)
Hunig's Base
Pd, CuI
Ph
N
N
X
CO2H
(6): X = O
(8): X = S

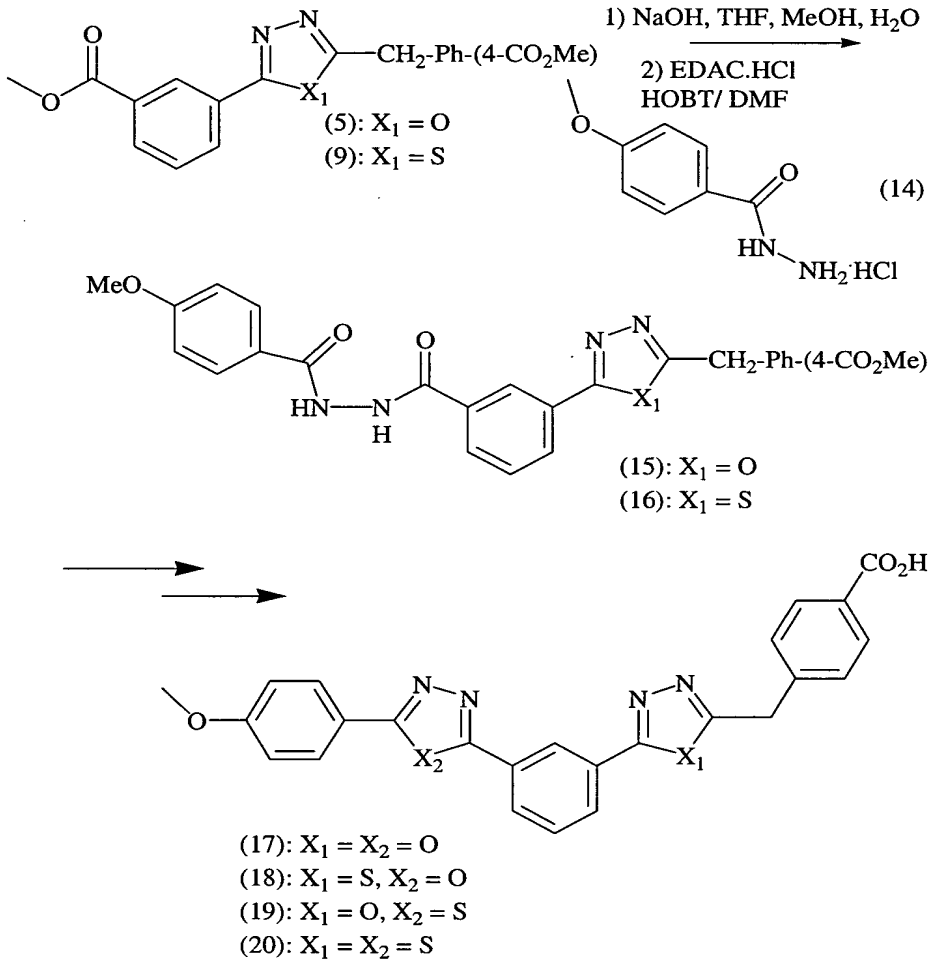
Scheme 8.


HO2C
CN
(1)
OCH3
HCl·H2N
O
(2)
CH3O
O
N
H
CN
(3)
N
N
N
(4)
CH3O
X
(5): X = O
(8): X = S
Br
1)
(6)
CO2t-Bu
, Cs2CO3
CO2H
2) TFA, DCM
(7): X = O
(9): X = S

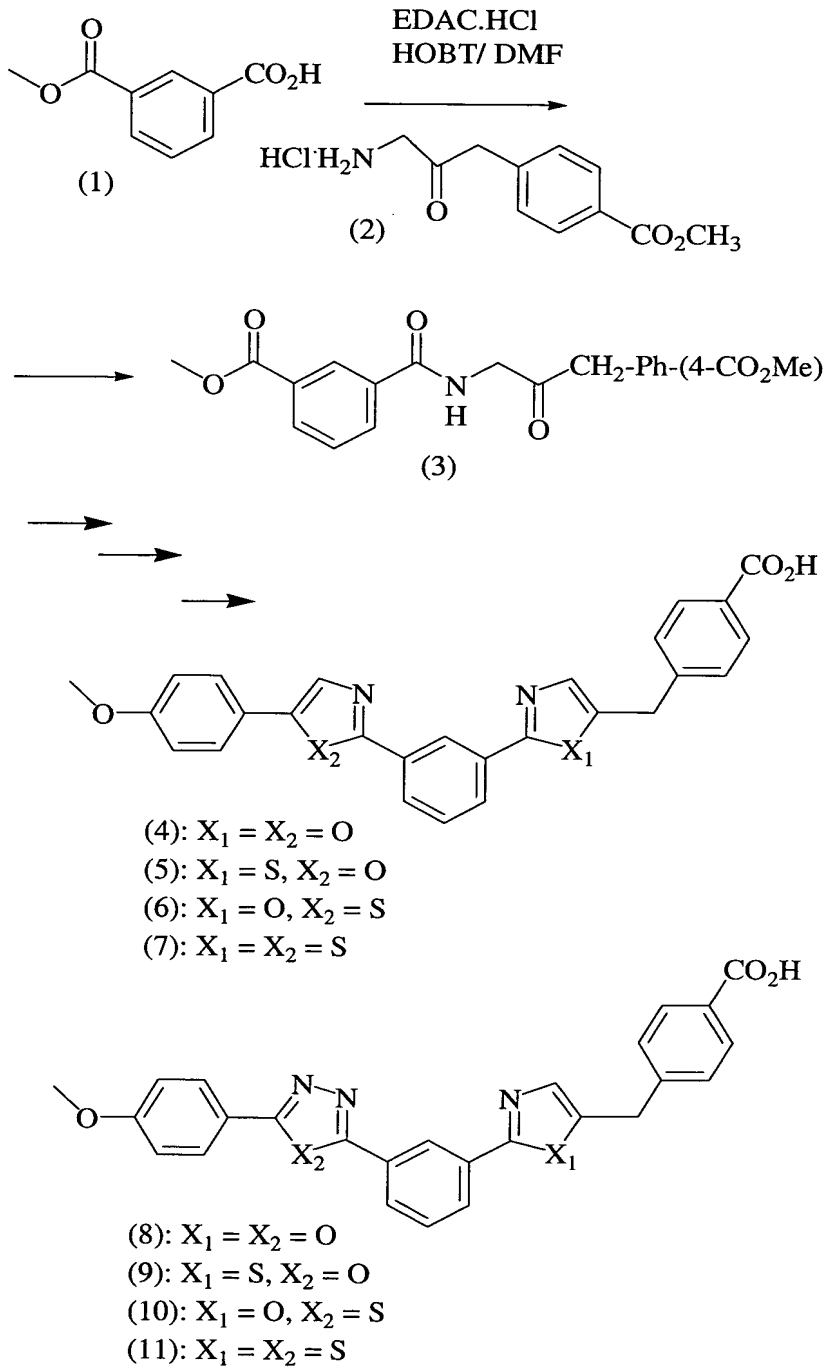
Scheme 9.


1. NH2NHBOC
EDAC.HCl/ HOBT
2. HCl (g)/ EtOAc
(1)
(2)
HCl
EDAC.HCl
HOBT/ DMF
4-(MeO2C)-PhCH2CO2H
(3)
(4)
CH2-Ph-(4-CO2Me)
PPA
(5): X1 = O
(9): X1 = S
1) NaOH, THF, MeOH, H2O
2) EDAC.HCl
HOBT/ DMF
(6)
NH2·HCl
(7): X1 = O
(10): X1 = S
1. PPA
2. NaOH, THF, MeOH
H2O
(8): X1 = X2 = O
(11): X1 = S, X2 = O
(12): X1 = O, X2 = S
(13): X1 = X2 = S

Scheme 9a.

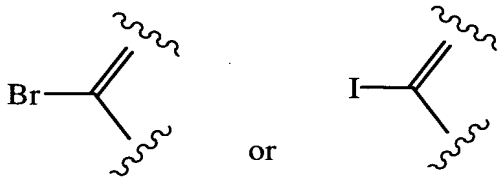

1) NaOH, THF, MeOH, H2O
2) EDAC.HCl
HOBT/ DMF
CH2-Ph-(4-CO2Me)
(5): X1 = O
(9): X1 = S
(14)
NH2·HCl
MeO
HN
N
H
CH2-Ph-(4-CO2Me)
(15): X1 = O
(16): X1 = S
CO2H
(17): X1 = X2 = O
(18): X1 = S, X2 = O
(19): X1 = O, X2 = S
(20): X1 = X2 = S

Scheme 10.



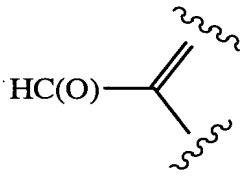
It should be appreciated that when Q is trans-(H)C=C(H), cis-(H)C=C(H), C≡C, $CH_2C{\equiv}C$, or $CF_2C{\equiv}C$ and is bonded to a sp^2 carbon atom in Formula I, a palladium catalyzed coupling of the corresponding terminal olefin or alkyne of formulas R^1-(trans-(H)C=CH_2), R^1-(cis-(H)C=CH_2), R^1-C≡CH, R^1-$CH_2C{\equiv}CH$, or

R^1-$CF_2C{\equiv}CH$, wherein R^1 is as defined above, with a bromo- or iodo-substituted sp^2 carbon atom of formula:



in the presence of a suitable base will yield a compound of Formula I wherein Q is trans-(H)C=C(H), cis-(H)C=C(H), C≡C, $CH_2C{\equiv}C$, or $CF_2C{\equiv}C$ and D is a group that is bonded to Q at a sp^2 carbon atom, and R^1, V, and R^2 are as defined above for Formula I. Illustrative examples of the coupling reagents and catalysts include palladium tetrakis(triphenylphosphine) or palladium(II) acetate as catalyst, a tertiary organic amine base such as triethylamine or diisopropylethylamine, a suitable solvent such as dimethylformamide ("DMF") or tetrahydrofuran ("THF"), and optionally a co-catalyst such as copper(I)iodide, at a suitable temperature such as from 0°C to 100°C, for a suitable time such as from 30 minutes to 2 days, and under an inert atmosphere such as an atmosphere of nitrogen or argon gas.

Alternatively, a corresponding aldehyde of formula



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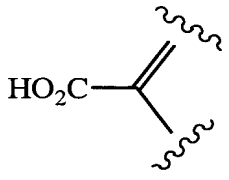
prepared as described below, may be coupled with a phosphonium ylide under Wittig olefination, or Horner-Emmons olefination, conditions to give a compound of Formula I wherein Q is trans-(H)C=C(H).

The bromo or iodo intermediates described above may be converted by conventional means to the corresponding carboxylic acid of formula



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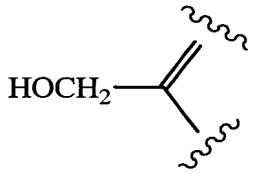
and the carboxylic acid converted by conventional means to compounds of Formula I wherein Q is OC(O), $CH(R^6)C(O)$, $OC(NR^6)$, $CH(R^6)C(NR^6)$,

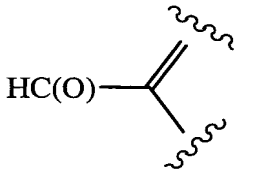
$N(R^6)C(O)$, $N(R^6)C(S)$, $N(R^6)C(NR^6)$, $SC(O)$, $CH(R^6)C(S)$, or $SC(NR^6)$. Illustrative examples include coupling of the carboxylic acid with an amine to provide a compound of Formula I wherein Q is $N(R^6)C(O)$, and optionally sulfurating the resulting amide with, for example P_2S_5 to provide a compound of Formula I wherein Q is $N(R^6)C(S)$. Alternatively, the carboxylic acid may be coupled with an alcohol to provide a compound of Formula I wherein Q is OC(O).

Alternatively, the carboxylic acid may be reduced to the corresponding hydroxymethyl compound of formula



and the hydroxymethyl converted to a compound of Formula I wherein Q is OCH_2 or $N(R^6)CH_2$ by conventional means.

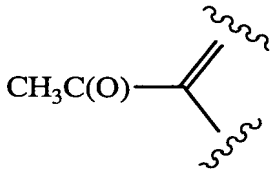
Alternatively, the hydroxymethyl compound may be oxidized to the corresponding aldehyde of formula



and the aldehyde coupled with hydroxylamine to give a corresponding oxime. The oxime may be chlorinated, and the chlorooxime cyclized with an olefin or alkyne to give a compound of Formula I wherein Q is a 5-membered heteroarylene.

Alternatively, the aldehyde may be prepared from the corresponding carboxylic acid by coupling the carboxylic acid with N,O-dimethylhydroxylamine and reducing the resulting dimethylhydroxamide with a suitable hydride reducing agent such as sodium borohydride or lithium aluminum hydride.

Alternatively, the above-described carboxylic acid intermediate may be converted by conventional means to the corresponding methyl ketone of formula



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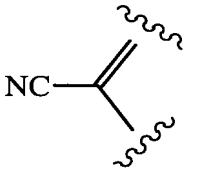
and the methyl ketone may be halogenated on methyl and coupled with various amines, alcohols, or other halogenated compounds to give a compound of Formula I wherein Q is $CH(R^6)C(O)$.

Alternatively, the above-described carboxylic acid intermediate or bromo- or iodo-intermediates may be converted by conventional means to the corresponding nitrile of formula



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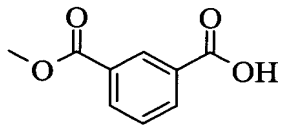
and the nitrile condensed with an amine or alcohol under non-nucleophilic basic conditions (e.g., 1,8-diazaundecane) to give a compound of Formula I wherein Q is $N(R^6)C(NR^6)$ or $OC(NR^6)$, respectively.

Alternatively, compounds of Formula I wherein Q is a lactam diradical may be prepared by conventional means by cyclizing the corresponding gamma-amino acids.

The synthesis of certain intermediates are described below in the Preparations.

PREPARATION 1

Synthesis of isophthalic acid monomethyl ester



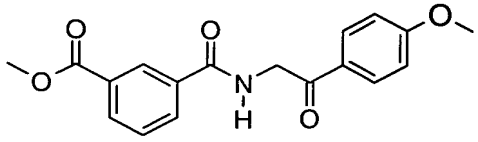
The following were introduced into a vessel: 10.0g (40.3 mmol) of methyl 3-bromobenzoate, 2.5g (mmol) of 1,3-bis(diphenylphosphino)propane ("DPPP"), 14 mL of triethylamine, 0.905 g of palladium acetate, and 140 ml of methanol. The vessel was sealed and pressurized with carbon monoxide to a pressure of 500

psi. The vessel was heated to 100 °C for 15 hours. The mixture was then cooled and concentrated on a rotary evaporator before partitioning between EtOAc and 2M HCl. The layers were separated, and the aqueous layer was extracted with EtOAc (1x). The organic extracts were combined and washed with saturated aqueous NaCl solution and dried ($MgSO_4$). Concentration provided a solid, which is slurried in hexane and filtered. The material is dried in a vacuum oven at ~ 10mmHg at 70 °C; yield 5.9g (82%).

NMR: DMSO ^1H δ (ppm) 3.54 (3H, s); 7.18-7.21 (1H, m); 7.34- 7.40 (1H, m); 7.46- 7.49 (1H m); 7.87- 7.89 (1H, m).

PREPARATION 2

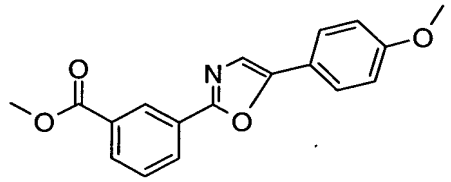
Synthesis of N-[2-(4-Methoxy-phenyl)-2-oxo-ethyl]-isophthalamic acid methylester



1.8 g (5.5 mmol) of isophthalic acid monomethyl ester from Preparation 1, 3.5g (18.5 mmol) of EDAC·HCl, 2.5g (18.5 mmol) of HOBt, and 3.1 g (15.4 mmol) of 2-amino-1-(4-methoxy-phenyl)-ethanone hydrochloride were dissolved in 20 mL of dimethylformamide. 1.9g (15.4 mmo l) of di-isopropyl ethylamine was then added. Stirring was continued overnight at room temperature. Water (60 ml) was added, and the product was filtered, washed with water. The resulting solid was triturated in hot methanol, filtered and dried in a vacuum oven overnight at 70 °C to provide 3.5 g (69%) desired product. MS: m/z (APCI, AP+) 328 $[M^{\cdot}]^+$ NMR: DMSO ^1H δ (ppm) 3.84 (3H, s); 3.88 (3H, s); 4.73 (2H, d, *J = 5.6 Hz*); 7.04- 7.08 (2H m); 7.63-7.66 (1H, t, *J = 7.8 Hz*);7.99- 8.027 (2H, m); 8.097-8.16 (2H,m); 8.47-8.48 (1H,m); 9.00-9.03 (1H, t, *J = 5.8 Hz*).

PREPARATION 3

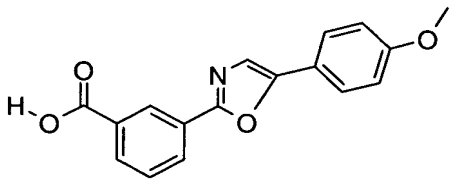
Synthesis of 3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoic acid methyl ester



0.5 g 1.5 mmol) of N-[2-(4-Methoxy-phenyl)-2-oxo-ethyl]-isophthalamic acid methylester from Preparatino 2 was dissolved in ~15 mL of poly phosphoric acid. The mixture was stirred at 80 °C for 2 hours before allowing it to cool to room temperature. Water (60 mL) was added, and the product precipitated upon agitation. The solid was filtered and washed with water. Slurried solid product in hot methanol and filtered. Dried in vacuum oven overnight to obtain 0.38 (80%) desired product.

PREPARATION 4

Synthesis of 3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoic acid



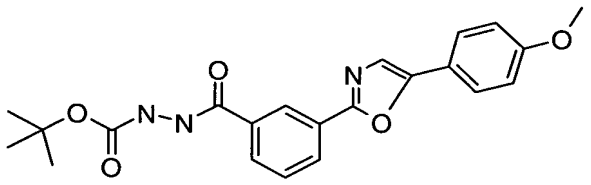
A solution of 1.7g (5.5mmol) N-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-isophthalamic acid methylester from Preparation 3 in a 3:1:1 mixture of THF/ methanol/ water was added 10mL (10 mmol) 1N NaOH. The mixture was stirred 4 hours at room temperature before concentrating on a rotary evaporator. The residue was treated with 6M HCl then filtered, washed with water (1X) and dried in a vacuum oven overnight at 70 °C to provide 1.5 g (91%) desired product.

MS: m/z (APCI, AP+) 296 $[M^{\cdot}]^{+}$

NMR: DMSO ^{1}H δ (ppm) 3.79 (3H, s); 7.03-7.07 (2H, m); 7.65- 7.79 (4H, m); 8.03- 8.06 (1H m); 8.26- 8.28 (1H m); 8.54- 8.55 (1H, m).

PREPARATION 5

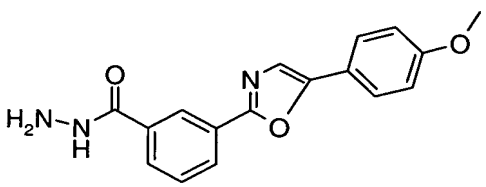
Synthesis of N'-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoyl}-hydrazinecarboxylic acid tert-butyl ester



1.5 g (5.0 mmol) of 3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoic acid from Preparation 4, 1.3g (6.6 mmol) EDAC·HCl, 0.89g (6.6 mmol) HOBT, and 0.87 g (6.6 mmol) hydrazinecarboxylic acid tert-butyl ester was dissolved in 20 mL of dimethylformamide. Stirring was continued 48 hours at room temperature. Water (60 mL) was added, and the product was extracted with 1:1 THF/ EtOAc (2x). Combined the organic extracts and washed with saturated aqueous NaCl solution (3x), dried ($MgSO_4$). Dried in a vacuum oven overnight at 70 °C to provide 1.6 g (82%) of desired product. MS: m/z (APCI, AP+) 410 $[M^{\cdot}]^+$ NMR: DMSO ^1H δ (ppm) 1.48 (9H, s); 3.84 (3H, m); 6.93-6.96 (2H, m); 7.25-7.29 (2H m); 7.36-7.53 (2H, m); 7.60-7.63 (1H, m); 7.69-7.92; 8.00 (1H, s); 8.16-8.48 (1H, m).

PREPARATION 6

Synthesis of 3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoic acid hydrazide



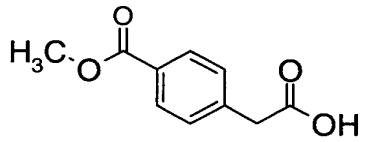
To a 0 °C suspension of 2.0g (5.0 mmol) N'-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoyl}-hydrazinecarboxylic acid tert-butyl ester from Preparation 5 in 30 mL EtOAC was bubbled HCl gas for 3 minutes. Gas flow was stopped and

the mixture was stirred 2 hours. The solid product was filtered off and washed with EtOAc. Dried in a vacuum oven at 70 °C overnight to obtain 1.5 g (96%) desired white solid. MS: m/z (APCI, AP+) $[M^{\cdot}]^{+}$

NMR: DMSO ^{1}H δ (ppm) (9H, s); (3H, m); (2H, m); (2H m); (2H, m); (1H, m); 8 (1H, s).

PREPARATION 7

Synthesis of 4-Carboxymethyl-benzoic acid methyl ester



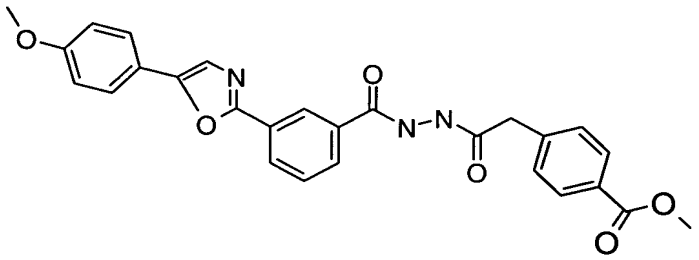
30.0g (139 mmol) of (4-Bromo-phenyl)-acetic acid 5.7g (14 mmol) DPPP, 32.4 mL of triethylamine, 2.08 g palladium acetate and 300 mL of methanol were introduced into a vessel. The vessel was sealed and pressurized with carbon monoxide to a pressure of 500psi. The vessel was heated at 100 °C for 15 hours. The mixture was then cooled and concentrated on a rotary evaporator before partitioning between EtOAc and 2M HCl. Separated and extracted the aqueous layer with EtOAc (1x). The organic extracts were combined and washed with saturated aqueous NaCl solution and dried (MgSO4). Concentration provided a solid which was slurried in hexane and filtered. The material was dried in a vacuum oven at ~ 10mmHg at 70 °C; yield 24 g (88%)

MS: m/z (APCI, AP^{-}) 179 $[M^{\cdot}]^{-}$

NMR: DMSO ^{1}H δ (ppm) 3.86 (3H, s); 7.63-7.67 (1H, m); 8.15- 8.18 (2H, m); 8.45-8.46 (1H m).

PREPARATION 8

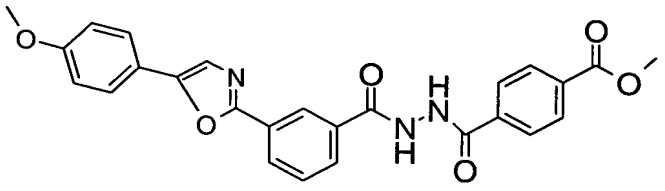
Synthesis of 4-[2-(N'-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoyl}-hydrazino)-2-oxo- ethyl]-benzoic acid methyl ester



0.7 g (2.0 mmol) of 3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoic acid hydrazide hydrochloride from Preparation 6, 0.49g (2.6 mmol) EDAC·HCl, 0.35g (2.6 mmol) HOBT, and 0.50 g (2.6 mmol) 4-carboxymethyl-benzoic acid methyl ester from Preparation 7 was dissolved in 20 mL of dimethylformamide. 0.33g (2.6 mmol) Di-isopropylethylamine was then added. Stirring was continued 14 hours at room temperature. Water (60 ml) was added and the product was extracted with 1:1 Et_2O/ EtOAc (2x). Combined the organic extracts and washed with saturated aqueous NaCl solution (4x), dried ($MgSO_4$). The resulting solid was triturated in EtOAc and filtered. Dried in a vacuum oven overnight at 70 °C to provide 0.48 g (49%) desired product. MS: m/z (APCI, AP+) 486 $[M^{\cdot}]^+$
NMR: DMSO ^1H δ (ppm) 3.66 (2H, s); 3.79 (3H, s); 3.83 (3H, s); 7.04-7.08 (2H, m); 7.48-7.50 (2H,m); 7.53-7.98 (9H, m); 7.99-8.24 (1H, m); 8.52-8.53 (1H, m).

PREPARATION 9

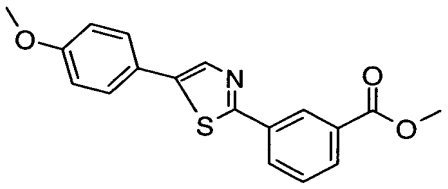
Synthesis of 4-(N'-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoyl}-hydrazinocarbonyl)-benzoic acid methyl ester



Using the procedure from Preparation 8 and terephthalic acid monomethyl ester in place of 4-carboxymethyl-benzoic acid methyl ester from Preparation 7 was obtained 0.48g (50%) of desired white solid. MS: m/z (APCI, AP+) 472 $[M^{\cdot}]^+$ NMR: DMSO ^1H δ (ppm) 3.77 (3H, s); 3.85 (3H, S); 7.03-7.05 (2H, d); 7.66- 7.78 (4H, m); 8.00-8.07 (5H, m); 8.23- 8.25 (1H, d); 8.56 (1H, s); 10.77-10.81 (2H, broad m).

PREPARATION 10

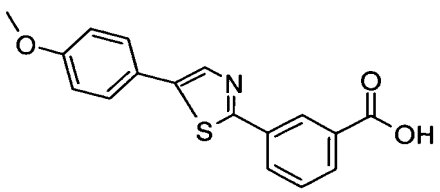
Synthesis of 3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-benzoic acid methyl ester



To a suspension of 1.4 g (4.3 mmol) N-[2-(4-Methoxy-phenyl)-2-oxo-ethyl]-isophthalamic acid methylester from Preparation 2 in 30 mL of dry dioxane was added 1.1g (5.2 mmol) of P_2S_5 in one portion. The resulting mixture was warmed to 50 °C for 1 hour before cooling to room temperature and adding about 60 ml water. Stirred 2 hours and then filtered off solid product. Triturated in hot MeOH and filtered. Dissolved in THF and filtered through a plug of flash silica gel with THF eluent. Concentration gave 1.4g (100%) of desired product. Used directly in the procedure of Preparation 11 without characterization.

PREPARATION 11

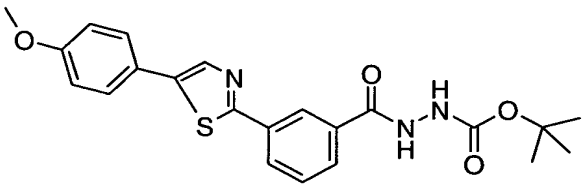
Synthesis of 3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-benzoic acid



A solution of 1.4g (4.3mmol) 3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-benzoic acid methyl ester from Preparation 10 in a 3:1:1 mixture of THF/ methanol/ water was added 10mL (10 mmol) 1N NaOH. The mixture was stirred 14 hours at room temperature before concentrating on a rotary evaporator. The residue was treated with 6M HCl then filtered, washed with water (1X) and dried in a vacuum oven overnight at 70 °C to provide 1.2 g (88%) of desired product. MS: m/z (APCI, AP+) 312 $[M^{\cdot}]^{+}$ NMR: DMSO ^{1}H δ (ppm) 3.79 (3H, s); 7.00-7.07 (2H, m); 7.61- 7.67 (3H, m); 7.99-8.02 (1H, m); 8.14-8.17 (1H, m); 8.22- (1H, s); 8.44-8.45 (1H, m).

PREPARATION 12

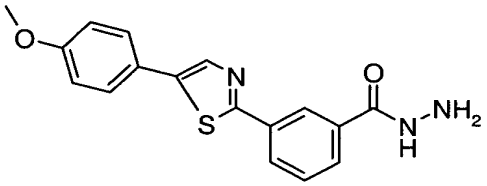
Synthesis of N'-{3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-benzoyl}-hydrazinecarboxylic acid tert-butyl ester



Using the procedure from Example B2 and 1.2g (3.8 mmol) 3-[5-(4-methoxy-phenyl)-thiazol-2-yl]-benzoic acid from Preparation 11 as starting material, the desired product was obtained.

PREPARATION 13

Synthesis of 3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-benzoic acid hydrazide hydrochloride

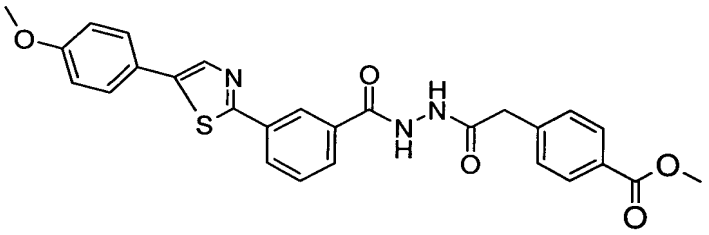


Using the procedure from Preparation 6 and 0.85g (2.0 mmol) N'-{3-[5-(4-methoxy-phenyl)-thiazol-2-yl]-benzoyl}-hydrazinecarboxylic acid tert-butyl ester from Preparation 12, 0.68g (45%) desired product was obtained.

MS: m/z (APCI, AP+) 326 $[M^{\cdot}]^+$ NMR: DMSO ^{1}H δ (ppm) 3.79 (3H, s); 7.01-7.05 (2H, m); 7.64- 7.74 (3H, m); 8.00-8.01 (1H, m); 8.03-8.18 (1H, m); 8.24-(1H, s); 8.45-8.46 (1H, m).

PREPARATION 14

Synthesis of 4-[2-(N'-{3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-benzoyl}-hydrazino)-2-oxo-ethyl]-benzoic acid methyl ester



Using the procedure from Preparation 8 and 0.67 (2.1 mmol) 3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-benzoic acid hydrazide hydrochloride from Preparation 13 0.35 (33%) of desired product was obtained. MS: m/z (APCI, AP+) 502 $[M^{\cdot}]^+$ NMR: DMSO ^{1}H δ (ppm) 3.65 (2H, S); 3.79 (3H, s); 3.83 (3H, s); 7.00-7.04 (2H, m); 7.48- 7.67 (5H, m); 7.90-7.95 (3H, m); 8.11-8.13 (1H, m); 8.24 (1H, s); 8.40-8.41 (1H, m).

Illustrative examples of the synthesis of compounds of Formula I are described below in the Examples.

EXAMPLE 1

Step (a): 3-(2H-Tetrazol-5-yl)benzoic acid methyl ester

To a solution of 3-cyanobenzoic acid (12.3 g, 0.083 mol) in toluene (300 mL) were added sodium azide (16 g, 0.25 mol) and triethylamine hydrochloride (34 g, 0.25 mol) respectively. The reaction mixture was refluxed for 4 hours, cooled to room temperature, and diluted with water (300 mL). The organic phase

was separated and the aqueous portion was acidified (pH=1) using concentrated HCl. The precipitate was collected by filtration and oven-dried to give 14 g (89%) of the tetrazole as a white solid. CI-MS: C8H6N4O2 [M+1] 191.0. The product obtained (14 g, 0.074 mol) was suspended in anhydrous methanol followed by the addition of gaseous HCl over a period of 20 minutes. The warm solution was stirred at room temperature for overnight, then concentrated in vacuo. The resulting residue was triturated with diethyl ether and collected by filtration to yield 12.1 g (81%) of the methyl ester intermediate 2. CI-MS: C9H8N4O2 [M+1] 205.2

Step (b): 3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoic acid methyl ester

The methyl ester synthesized in Step (a) (12.1 g, 0.059 mol) was diluted with acetonitrile (300 mL) and triethylamine (6.6 g, 0.060 mol). Dissolution occurred after stirring at room temperature for 5 minutes. The solution was treated with 4-methoxybenzyl chloride (6.6 g, 0.065 mol) and refluxed for overnight. Precipitation occurred on cooling the reaction mixture to room temperature. The solvent was concentrated and the residue was triturated with ethyl acetate and filtered. The filtrate was washed with aqueous HCl (1M, 50 mL), dried (MgSO4), and concentrated in vacuo. The 2-isomer was isolated analytically pure utilizing silica gel chromatography (elution with dichloromethane) to give the title compound (10.5 g, 55%) as a white solid. ^{1}HNMR (CDCl3) δ 8.8 (s, 1H), 8.3 (d, 1H), 8.1 (d, 1H), 7.5 (t, 1H), 7.2 (d, 2H), 6.9 (d, 2H), 5.7 (s, 2H), 3.9 (s, 3H), 3.8 (s, 3H) ppm. Mp 105-106 °C.

Step (c): 3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoic acid

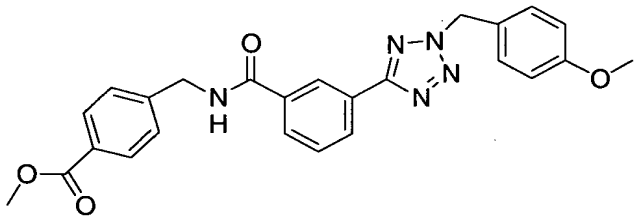
The ester prepared in Step (b) (10.4 g, 0.032 mol) was suspended in aqueous tetrahydrofuran (20 mL, 1:1) followed by the addition of lithium hydroxide monohydrate (4 g, 0.096 mol) in one portion. Dissolution occurred after stirring at room temperature for 30 minute. The solution was stirred for an additional 16 hours. The THF was concentrated in vacuo and the aqueous solution was acidified to pH=1 using concentrated HCl. The resulting precipitate was collected by filtration and recrystallized from hexane/ethyl acetate to give the title compound (10 g, 100%) as a white solid. ^{1}HNMR (DMSO-d6) δ 8.6 (s, 1H), 8.3

(d, 1H), 8.1 (d, 1H), 7.7 (t, 1H), 7.4 (d, 2H), 6.9 (d, 2H), 6.9 (s, 2H), 3.7 (s, 3H) ppm.

Step (d): 3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoyl chloride.

The carboxylic acid intermediate (10 g, 0.032 mol) from Step (c) was suspended in dichloromethane followed by the addition of oxalyl chloride (20.4 g, 0.16 mol) and catalytic DMF. The reaction mixture was stirred at room temperature for 3 hours, at which time dissolution was nearly complete. The reaction mixture was filtered and concentrated in vacuo. The residue was triturated with petroleum ether and collected by filtration to give the title compound (9.5 g, 90%) as a white solid. ^{1}HNMR (CDCl3) δ 8.9 (s, 1H), 8.5 (d, 1H), 8.2 (d, 1H), 8.6 (t, 1H), 7.4 (d, 2H), 6.9 (d, 2H), 3.8 (s, 3H) ppm. Mp 122-124 °C.

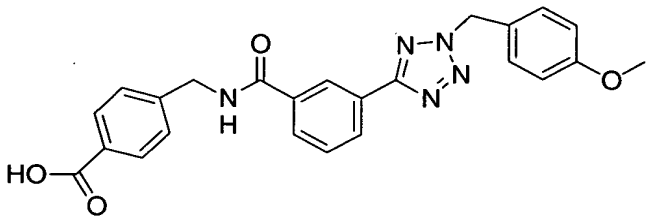
Step (e): 4-({3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester



To a solution of methyl 4-(aminomethyl)benzoate hydrochloride (0.22 g, 1.1 mmol) and triethylamine (0.22 g, 2.2 mmol) in dichloromethane (20 mL) was added the acid chloride (0.33 g, 1.01 mmol) prepared in (e). The reaction mixture was stirred at room temperature for 16 hour, then diluted with aqueous HCl (1M, 20 mL). The organic phase was separated, washed with brine, dried (MgSO4), and concentrated in vacuo. The residue was recrystallized from hexane/ethyl acetate to give a white solid (0.38 g, 83%). ^{1}HNMR (DMSO-d6) δ 9.4 (t, 1H), 8.5 (s, 1H), 8.2 (d, 1H), 8.1 (d, 1H), 7.9 (d, 2H), 7.8 (t, 1H),7.5 (d, 2H), 7.4 (d, 2H), 6.9 (d, 2H), 5.9 (s, 2H), 4.5 (d, 2H), 3.8 (s, 3H), 3.7 (s, 3H) ppm. Mp 167-168 °C.

EXAMPLE 2

4-({3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid

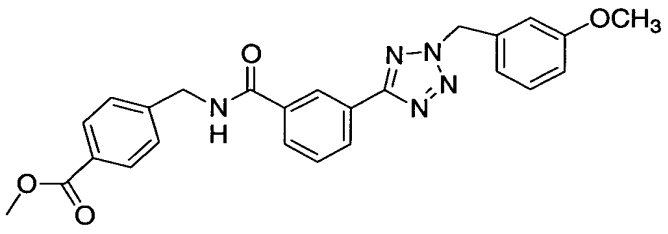


The ester (0.065 g, 0.14 mmol) prepared in Example 1, Step (e) was diluted with aqueous tetrahydrofuran followed by the addition of lithium hydroxide monohydrate (0.018 g, 0.4 mmol). Following the experimental conditions described in (d) yielded the free acid (0.045 g, 71%)as a white solid. ^{1}HNMR (DMSO-d6) δ 12.8 (bs, 1H), 9.4 (t, 1H), 8.5 (s, 1H), 8.2 (d, 1H), 8.0 (d, 1H), 7.9 (d, 2H), 7.7 (t, 1H), 7.4 (dd, 4H), 6.9 (d, 2H), 5.9 (s, 2H), 4.5 (d, 2H), 3.7 s, 3H) ppm. Mp 202-205 °C.

Replacement of 4-methoxybenzyl chloride in Step (b) of Example 1 with an appropriately substituted alkyl halide and utilizing the experimental conditions described for Example 1 and Example 2 yielded the following compounds:

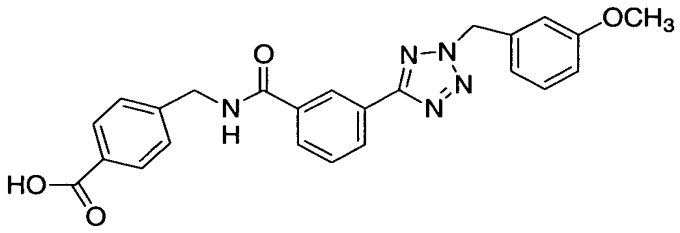
EXAMPLE 3

4-({3-[2-(3-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester. Mp 153-154 °C.



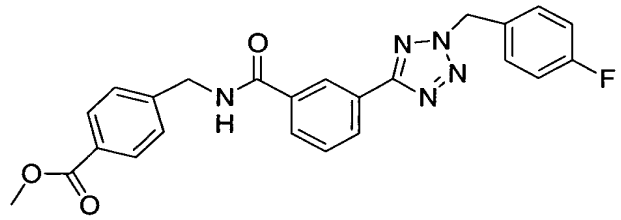
EXAMPLE 4

4-({3-[2-(3-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid. Mp 204-206 °C.



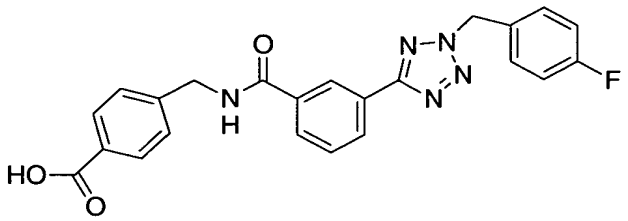
EXAMPLE 5

4-({3-[2-(4-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester. Mp 179-178 °C.



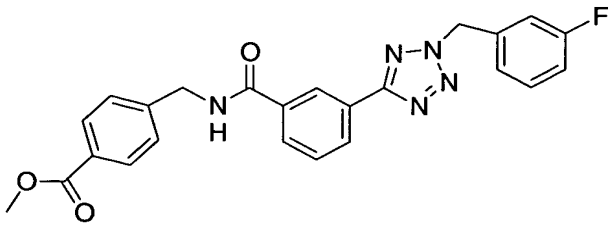
EXAMPLE 6

4-({3-[2-(4-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid. Mp 222-224 °C.



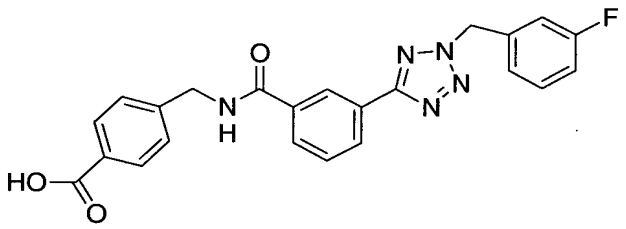
EXAMPLE 7

4-({3-[2-(3-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid methyl ester. Mp 157-155 °C.



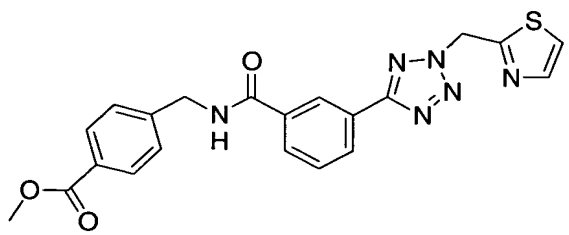
EXAMPLE 8

4-({3-[2-(3-Fluoro-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid. Mp 217-219 °C.



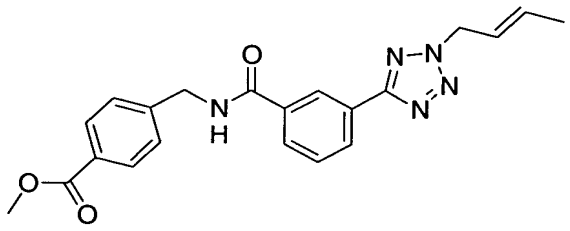
EXAMPLE 9

4-{[3-(2-Thiazol-2-ylmethyl-2Htetrazol-5-yl)-benzoylamino]-methyl{-benzoic acid methyl ester. Mp 158-160 °C.



EXAMPLE 10

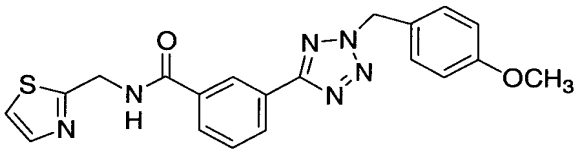
4-{[3-(2-But-2-enyl-2H-tetrazol-5-yl)-benzoylamino]-methyl}benzoic acid methyl ester. Mp 107-108 °C.



Replacement of methyl 4-(aminomethyl)benzoate hydrochloride in Step (e) of Example 1 with an appropriately substituted amine and utilizing the experimental conditions described for Example 1 yielded the following compounds:

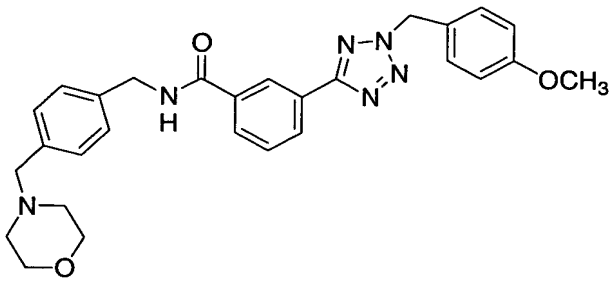
EXAMPLE 11

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-thiazol-2-ylmethyl-benzamide Mp 143-145 °C.



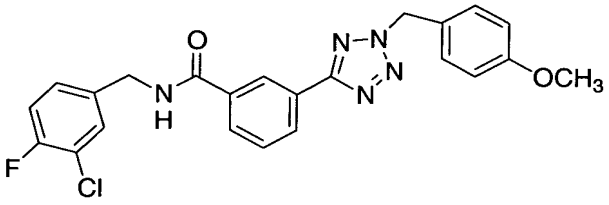
EXAMPLE 12

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(4-morpholin-4-ylmethyl-benzyl)-benzamide Mp 161-162 °C.



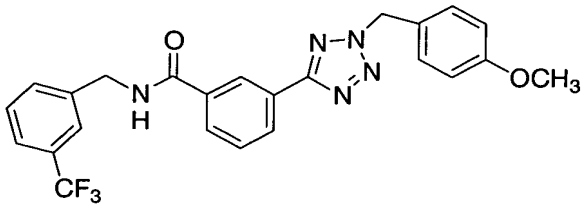
EXAMPLE 13

N-(3-Chloro-4-fluoro-benzyl)-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide Mp 150-151 °C



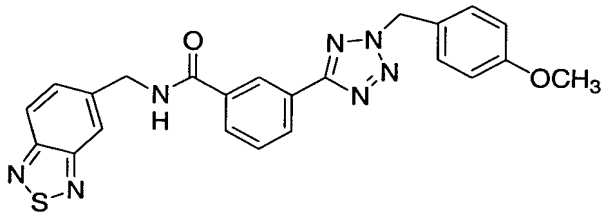
EXAMPLE 14

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(3-trifluoromethyl-benzyl)-benzamide Mp 162-163 °C.



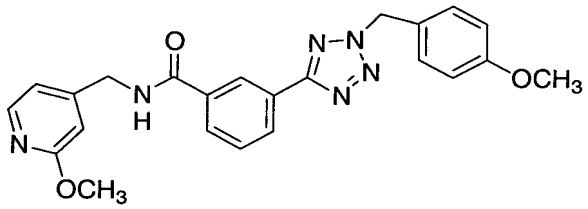
EXAMPLE 15

N-2,1,3-Benzothiadiazol-5-ylmethyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide Mp 207-208 °C.



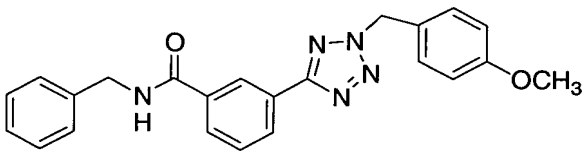
EXAMPLE 16

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(2-methoxy-pyridin-4-ylmethyl)-benzamide Mp 166-169 °C.



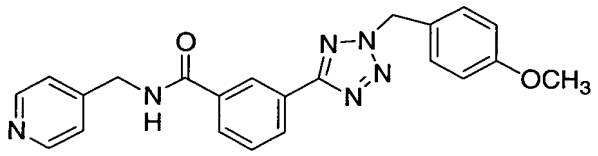
EXAMPLE 17

N-Benzyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide Mp 169-170 °C.



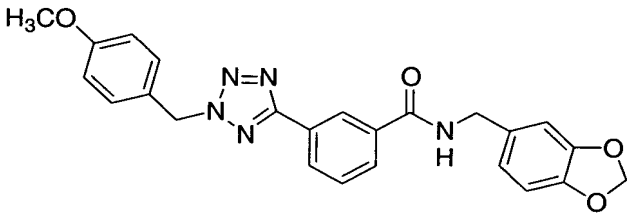
EXAMPLE 18

3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-pyridin-4-ylmethyl-benzamide Mp 163-164 °C.



EXAMPLE 19

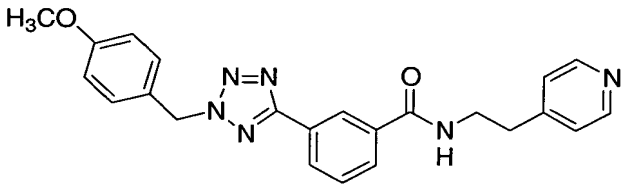
N-1,3-Benzodioxol-5-ylmethyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide.



LC/MS: MW 443.46, 94.69% purity

EXAMPLE 20

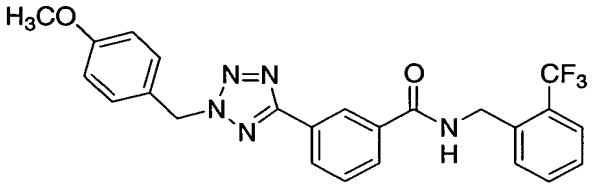
3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(2-pyridin-4-yl-ethyl)-benzamide.



LC/MS: MW 414.46, 100% purity

EXAMPLE 21

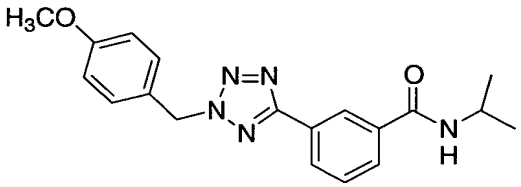
3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(2-trifluoromethyl-benzyl)-benzamide.



LC/MS: MW 467.45, 94.93% purity

EXAMPLE 22

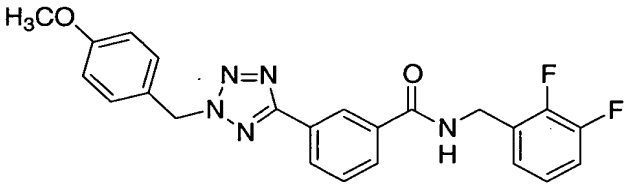
N-Isopropyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide.



LC/MS: MW 351.41, 96.37% purity

EXAMPLE 23

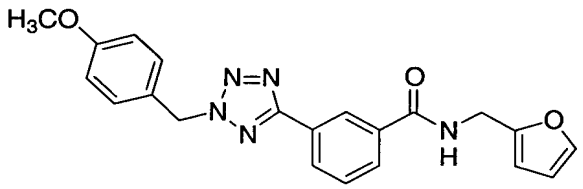
N-(2,3-Difluoro-benzyl)-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide.



LC/MS: MW 435.43, 100% purity

EXAMPLE 24

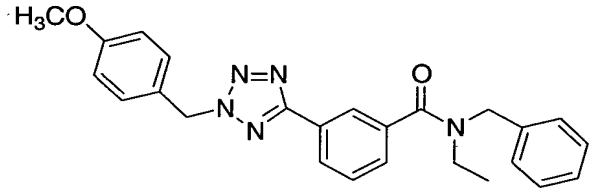
N-Furan-2-ylmethyl-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide.



LC/MS: MW 389.41, 100% purity

EXAMPLE 25

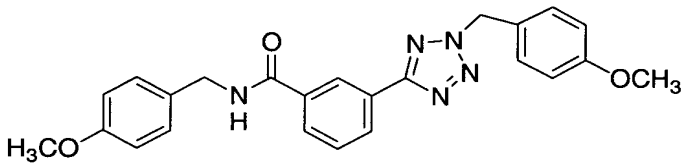
3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-N-(1-phenyl-ethyl)-benzamide.



LC/MS: MW 427.51, 100% purity

EXAMPLE 26

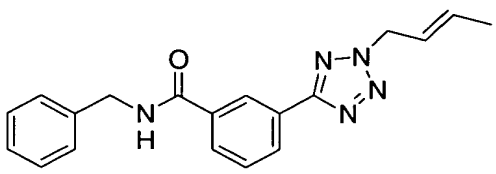
N-(4-Methoxy-benzyl)-3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide Mp 159-160 °C.



Replacement of 4-methoxybenyl chloride and methyl 4-(aminomethyl)benzoate hydrochloride in Steps (b) and (e) respectively of Example 1 with an appropriately substituted alkyl halide and amine, and utilizing the experimental conditions described for Example 1, yielded the following compounds:

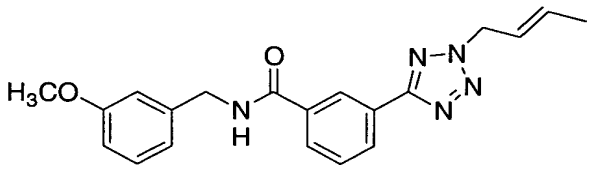
EXAMPLE 27

N-Benzyl-3-(2-but-2-enyl-2H-tetrazol-5-yl)-benzamide. Mp 100-101 °C.



EXAMPLE 28

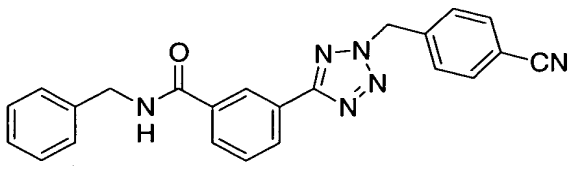
3-(2-But-2-enyl-2H-tetrazol-5-yl)-N-(3-methoxy-benzyl)-benzamide.



Elem. Anal. Calcd. For $C_{20}H_{21}N_5O_2$: C, 66.10%; H, 5.82%; N, 19.27%; Found: C, 66.00%; H, 5.78%; N, 19.23%.

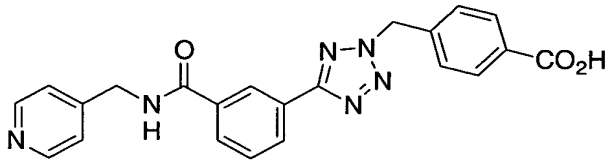
EXAMPLE 29

N-Benzyl-3-[2-(4-cyano-benzyl)-2H-tetrazol-5-yl]-benzamide. Mp 191-192 °C.



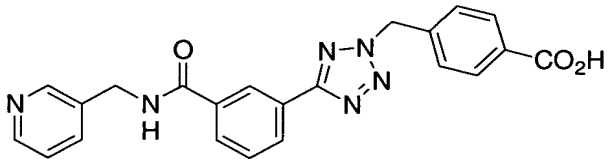
EXAMPLE 30

4-(5-{3-[(Pyridin-4-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid. TFA salt Mp 222°C dec.



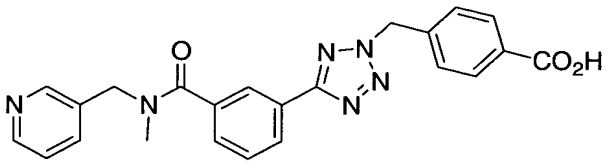
EXAMPLE 31

4-(5-{3-[(Pyridin-3-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid. TFA salt Mp 253°C dec.



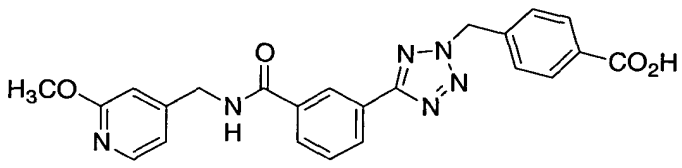
EXAMPLE 32

4-(5-{3-[(Methyl-pyridin-3-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid. TFA salt Mp 235°C dec.



EXAMPLE 33

4-(5-{3-[(2-Methoxy-pyridin-4-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid. TFA salt Mp 228°C dec.



EXAMPLE 34

N-(4-Fluoro-benzyl)-2-methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide.

Step (a): 5-(3-Bromo-4-methoxy-phenyl)-2H-tetrazole.

The same procedure was used to form the tetrazole as that which was described in Step (a) of Example 1. Yield: 9.9 g, 97%. ^{1}HNMR (DMSO-d6) δ 7.8 (s, 1H), 7.6 (d, 1H), 6.9 (d, 1H), 3.5 (s, 3H) ppm.

Step (b): 5-(3-Bromo-4-methoxy-phenyl)-2-(4-methoxy-benzyl)-2H-tetrazole

The tetrazole synthesized in Step (a) was alkylated using the experimental conditions described in Step (b) of Example 1. Yield: 8.6 g, 59%. ^{1}HNMR (CDCl3) δ 8.3 (s, 1H), 8.0 (d, 1H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 2H), 5.7 (s, 2H), 3.9 (s, 3H), 3.7 (s, 3H) ppm.

Step (c): 2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzoic acid methyl ester.

The tetrazole (4 g, 0.011 mol) prepared in Step (b) was added to a glass-lined reactor containing triethylamine (0.73 g, 0.03 mol), diphenylphosphinylpropane (0.66 g, 1.6 mmol), palladium (II) acetate (0.24 g, 1.1mmol), and anhydrous methanol (70 mL). The reaction mixture was heated to 100 °C under 500 psi carbon monoxide for 12 hours. The reaction mixture was filtered and thoroughly washed with tetrahydrofuran. The filtrate was concentrated in vacuo and the residue was recrystallized from hexane/ethyl acetate to give white crystalline needles (1.6 g, 43%). Mp 110-111 °C. ^{1}HNMR (CDCl3) δ 8.5 (s, 1H), 8.2 (d, 1H), 7.8 (m, 1H), 7.3-7.5 (m, 3H), 7.1 (d, 1H), 6.9 (d, 2H), 5.7 (s, 2H), 4.0 (s, 3H), 3.9 (s,3H), 3.8 (s, 3H) ppm.

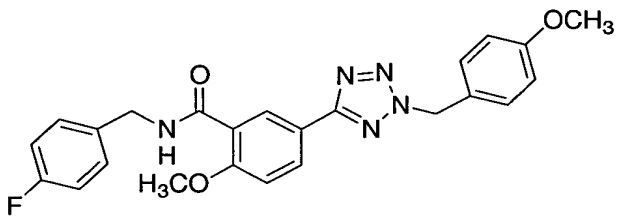
Step (d): 2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzoic acid.

The ester (0.91 g, 2.57 mmol) obtained in Step (c) was converted to the corresponding carboxylic acid utilizing reaction conditions described in step c of Example 1. Yield: 0.57 g, 65%. ^{1}HNMR (CDCl3) δ 8.9 (s, 1H), 8.3 (d, 1H), 7.4 (d, 2H), 7.2 (d, 1H), 6.9 (d, 2H), 5.7 (s, 2H), 4.1 (s, 3H), 3.8 (s, 3H) ppm.

Step (e): 2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzoyl chloride.

The acid chloride was prepared from the carboxylic acid (0.52g, 1.54 mmol, Step (d)) using reaction conditions previously described for step d of Example 1. The crude product (0.57 g, tan solid) was used without further characterization.

Step (f): N-(4-Fluoro-benzyl)-2-methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzamide.

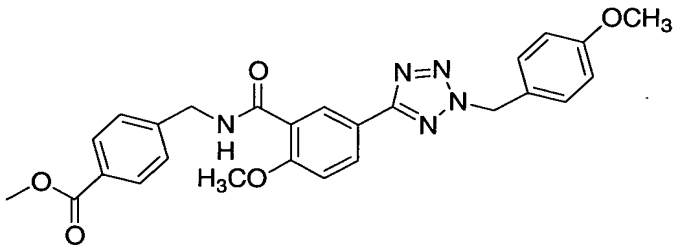


The crude acid chloride (0.2 g, 0.56 mmol) obtained in Step (e) was taken up in dichloromethane (2 mL) and added dropwise to a solution of 4-fluorobenzylamine (0.07 g, 0.56 mmol) and triethylamine (0.062 g, 0.61 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 16 hours, then diluted with aqueous HCl (1M, 5 mL). The organic phase was separated, dried (MgSO4), and concentrated in vacuo. The resulting solid was triturated with petroleum ether/diethyl ether (1:1) to yield a pale yellow solid (0.18 g, 72%). ^{1}HNMR (CDCl3) δ 8.9 (s, 1H), 8.3 (d, 1H), 8.1 (bs, 1H), 7.4 (d, 2H), 7.3 (m, 2H), 7.1 (m, 3H), 6.9 (d, 2H), 5.7 (s, 2H), 4.7 (d, 2H), 4.0 (s, 3H), 3.8 (s, 3H) ppm. Mp 156-158°C.

Replacement of 4-fluorobenzyl amine in Step (f) of Example 27 with an appropriately substituted amine yielded the corresponding tetrazole amide derivatives:

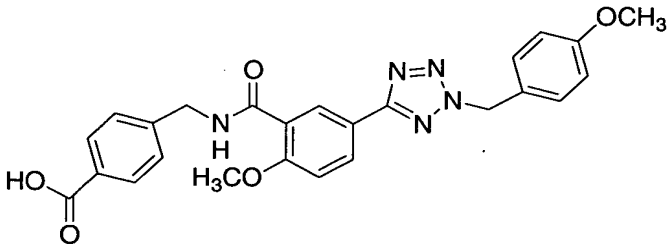
EXAMPLE 35

4-({2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid). Mp 177-178 °C.



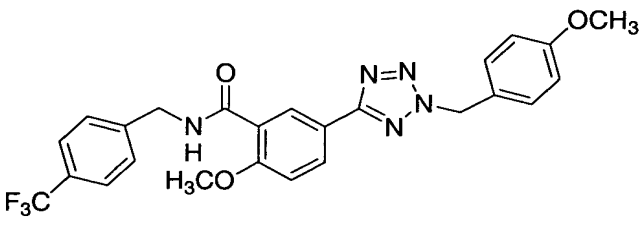
EXAMPLE 36

4-({2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid. Mp 207-209 °C.



EXAMPLE 37

2-Methoxy-5-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-N-(4-trifluoromethyl-benzyl)-benzamide. Mp 188-190 °C.



EXAMPLE 38

Benzyl{3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzyl}-amine hydrochloride.

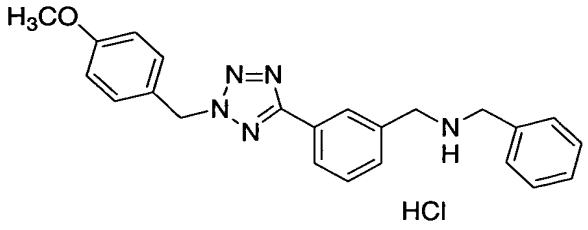
Step (a): {3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-phenyl}-methanol.

The acid chloride (2.5 g, 7.6 mmol) prepared in Step (d) of Example 1 was added to a suspension of lithium aluminum hydride ("LAH") (0.58 g, 25 mmol) in tetrahydrofuran (10 mL) cooled to 0 °C. The reaction mixture gradually warmed to room temperature over two hours. Aqueous HCl was added dropwise to quench excess LAH. The mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was washed with brine, dried (MgSO4), and concentrated. The resulting viscous liquid was triturated with hexane/diethyl ether to yield a pale yellow solid (1.9 g, 84%). Mp 70-72 °C.

Step (b): 5-(3-Bromomethyl-phenyl)-2-(4-methoxy-benzyl)-2H-tetrazole.

The alcohol (1 g, 3.37 mmol) of Step (a) was dissolved in dichloromethane (25 mL) and added dropwise at room temperature to a solution of phosphorous tribromide (1 g, 3.7 mmol) in dichloromethane (75 mL). The solution was stirred for 16 hours, then concentrated in vacuo. The residue obtained was triturated with hexane and collected by filtration to yield a white solid (1.17 g, 92 %). ^{1}HNMR (CDCl3) δ 8.2 (d, 1H), 7.7 (m, 2H), 7.5 (m, 1H), 7.4 (d, 2H), 6.8 (d, 2H), 5.8 (s, 2H), 4.5 (s, 2H), 3.7 (s, 3H) ppm.

Step (c): Benzyl{3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzyl}-amine hydrochloride.



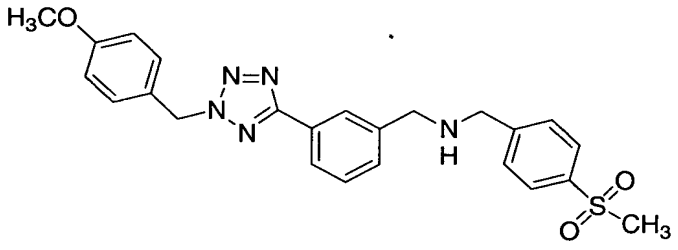
The alkyl halide (0.42 g, 1.06 mmol) prepared in Step (b) was dissolved in tetrahydrofuran (20 mL) followed by the addition of benzylamine (0.24 g, 2.2 mmol). The solution was refluxed for 16 hours, cooled to room temperature, and

concentrated in vacuo. The crude product was triturated with ethyl acetate, filtered, and the filtrate concentrated. The free base was isolated pure as a colorless liquid using silica gel chromatography (elution with dichloromethane/THF). The compound was taken up in diethyl ether and precipitated as the HCl salt upon treatment with gaseous HCl. The solid (0.25 g, 57%) was collected by filtration. Mp 159-161 °C.

If benzylamine in Step (c) of Example 38 is replaced with an appropriately substituted amine or alcohol, the following compounds will be obtained.

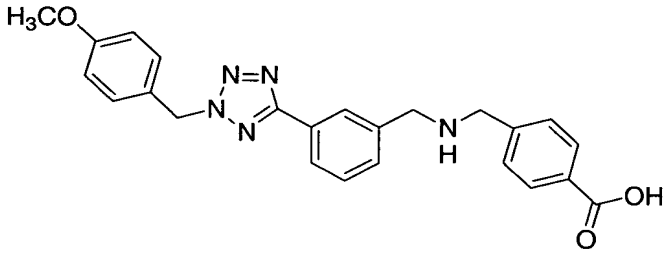
EXAMPLE 39

(4-Methanesulfonyl-benzyl)-{3-[2-(4-methoxy-benzyl)-2H-tetrazol-5-yl]-benzyl}-amine.



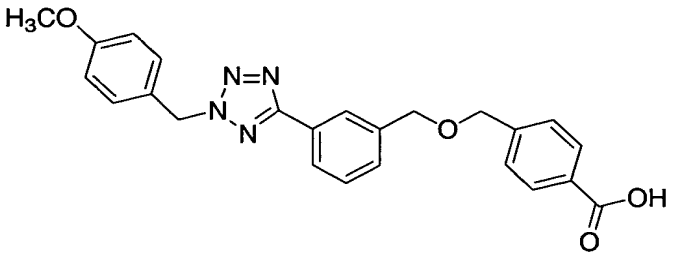
EXAMPLE 40

4-({3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5yl]-benzylamino}-methyl)-benzoic acid.



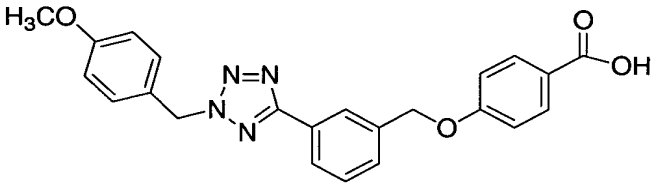
EXAMPLE 41

4-{3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzyloxymethyl}-benzoic acid.



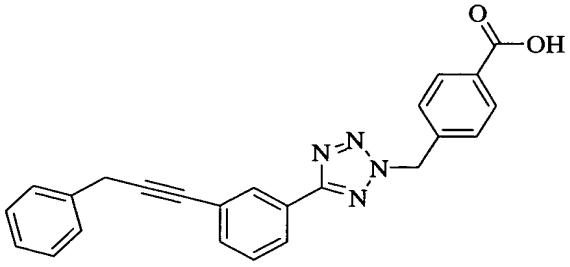
EXAMPLE 42

4-{3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzyloxy}-benzoic acid.



EXAMPLE 43

4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid.



Step (a): 5-(3-Iodo-phenyl)-2H-tetrazole.

The 3-iodobenzonitrile (3.6 g, 16.6 mmol) was converted to the corresponding tetrazole (4.1 g, 91%) utilizing reaction conditions previously described in Step (a) of example 1. CI-MS: $C_7H_5IN_2$ [M+1] 273.0.

Step (b): 4-[5-(3-Iodo-phenyl)-tetrazol-2-ylmethyl]-benzoic acid tert-butyl ester.

The tetrazole (4 g, 14.7 mmol) prepared in Step (a) was alkylated using the reaction conditions previously described in Step (b) of Example 1 to give analytically pure 2-regioisomer (3 g, 44%) and the 1-regioisomer (0.54 g, 8%) respectively. ^{1}HNMR (CDCl3) 2-regioisomer δ 8.5 (s, 1H), 8.1 (d, 1H), 8.0 (d, 2H), 7.8 (d, 1H), 7.4 (d, 2H), 7.2 (m, 2H), 5.8 (s, 2H), 1.6 (s, 9H) ppm. ^{1}HNMR (CDCl3) 1-regioisomer δ 8.0 (d, 2H), 7.9 (d, 2H), 7.5 (d, 1H), 7.3-7.1 (m, 3H), 5.6 (s, 2H) 1.6 (s, 9H) ppm.

Step (c): 4-[5-(3-Iodo-phenyl)-tetrazol-2-ylmethyl]-benzoic acid.

The ester (2.5 g, 5.41 mmol) prepared in Step (b) was suspended in dichloromethane (20 mL) followed by the addition of trifluoroacetic acid (5 mL). The solution was stirred for 16 hours at 25 °C, then concentrated in vacuo. The resulting white solid was triturated with hexane/diethyl ether and the carboxylic acid (2.1 g, 100%) was collected by filtration. Mp 241-242 °C.

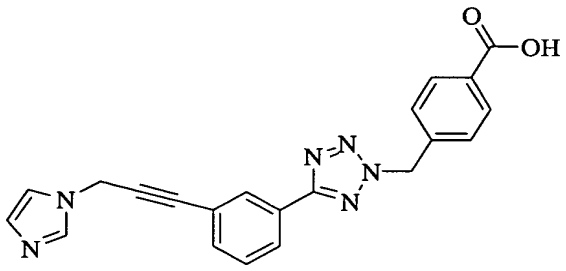
Step (d): 4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid.

The iodo derivative (1 g, 2.46 mmol) prepared in Step (c) was dissolved in dimethylformamide (10 mL) followed by the addition of diisopropylethylamine (1.3 g, 9.8 mmol), copper (I) iodide (0.17 g, 0.89 mmol), 3-phenyl-1-propyne (0.40 g, 3.4 mmol), and bis(triphenylphosphine) palladium (II) dichloride (0.34 g, 0.49 mmol). The reaction mixture was stirred at 50 °C for 4 hours under an atmosphere of N_2. The dark reaction mixture was cooled to room temperature and diluted with equal volumes of ethyl acetate and aqueous HCl. The organic phase was separated, washed with brine, dried (MgSO4) and concentrated in vacuo. The liquid obtained was purified using silica gel chromatography (elution with dichloromethane/tetrahydrofuran) to give a cream colored solid (0.37 g, 38%). Mp 195-198 °C. ^{1}HNMR (DMSO-d6) δ 13.0 (bs, 1H), 8.0-7.9 (m, 4H), 7.7-7.2 (m, 9H), 6.1 (s, 2H), 3.9 (s, 2H) ppm.

If 3-phenyl-1-propyne in Step (d) of Example 43 is replaced with an appropriately 3-substituted propyne, the following compounds will be obtained.

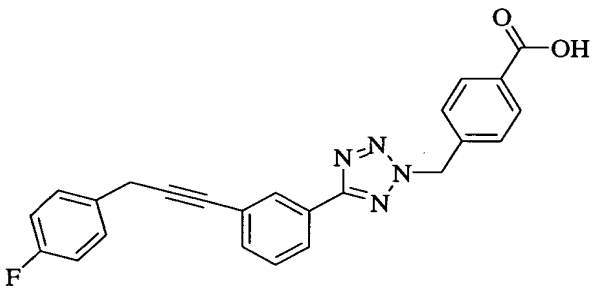
EXAMPLE 44

4-{5-[3-(3-Imidazol-1-yl-prop-1-ynyl)-phenyl]-terazol-2-ylmethyl}-benzoic acid.



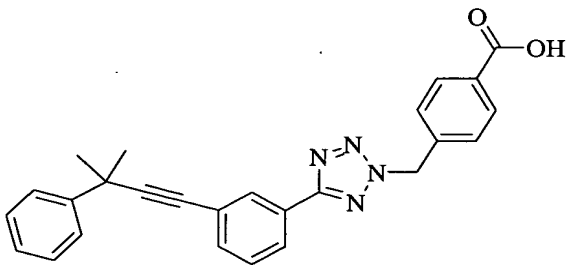
EXAMPLE 45

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid.



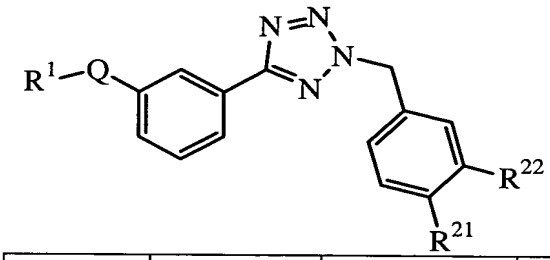
EXAMPLE 46

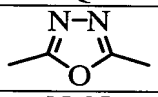
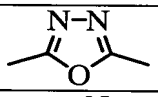
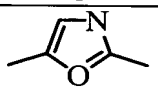
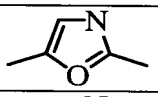
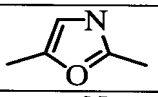
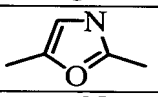
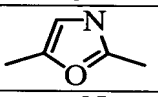
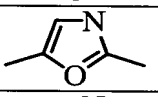
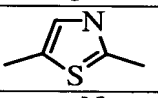
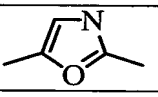
4-{5-[3-(3-Methyl-3-phenyl-but-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid.



The compounds of Example Table A beow were prepared according to the methods illustrated above in Schemes 6 to 10.

Example Table A.



Example No.	R^1	Q	R^{21}	R^{22}	Characterizing Data
A1	Benzyl ("Bn")		COOH	H	MS: m/z (APCI, AP+) 439 $[M^-]^+$
A2	Phenyl ("Ph")		COOH	H	MS: m/z (APCI, AP+) 425 $[M^-]^+$
A3	Ph		$COOC(CH_3)_3$	H	MS: m/z (APCI, AP+) 479 $[M^-]^+$
A4	Ph		COOH	H	MS: m/z (APCI, AP+) 424 $[M^-]^+$
A5	Ph		F	F	MS: m/z (APCI, AP+) 416 $[M^-]^+$
A6	4-CH_3O-Ph		$COOC(CH_3)_3$	H	MS: m/z (APCI, AP+) 510 $[M^-]^+$
A7	4-CH_3O-Ph		COOH	H	MS: m/z (APCI, AP+) 454 $[M^-]^+$
A8	4-CH_3O-Ph		F	F	MS: m/z (APCI, AP+) 446 $[M^-]^+$
A9	4-CH_3O-Ph		COOH	H	MS: m/z (APCI, AP+) 470 $[M^-]^+$
A10	4-Cl-Ph		COOH	H	MS: m/z (APCI, AP+) 490 $[M^-]^+$

The compounds of Example Table A have the following chemical names (Example No.):

4-{5-[3-(5-Benzyl-[1,3,4]oxadiazol-2-yl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid (A1);

4-{5-[3-(5-Phenyl-[1,3,4]oxadiazol-2-yl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid (A2);

4-{5-[3-(5-Phenyl-oxazol-2-yl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid tertiary butyl ester (A3);

4-{5-[3-(5-Phenyl-oxazol-2-yl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid (A4);

2-(3,4-Difluoro-benzyl)-5-[3-(5-phenyl-oxazol-2-yl)-phenyl]-2H-tetrazole (A5);

4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid tertiary butyl ester (A6);

4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid (A7);

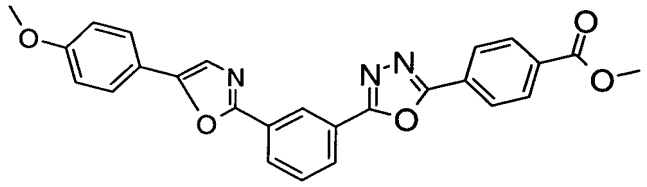
2-(3,4-Difluoro-benzyl)-5-{3-[5-(4-methoxy-phenyl)-oxazol-2-yl]-phenyl}-2H-tetrazole (A8);

4-(5-{3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid (A9); and

4-(5-{3-[5-(4-Chloro-phenyl)-oxazol-2-yl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid (A10).

EXAMPLE B1a

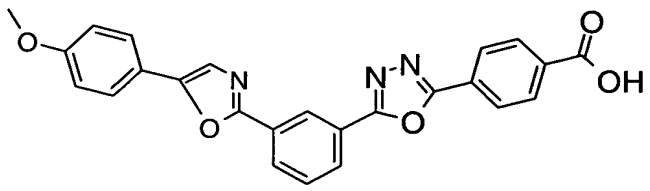
Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester



Using the procedure from Example B2a below and 4-(N'-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoyl}-hydrazinocarbonyl)-benzoic acid methyl ester from Preparation 9 as starting material 0.21g (48%) desired product was obtained. MS: m/z (APCI, AP+) 454 $[M^{\cdot}]^{+}$.

EXAMPLE B1

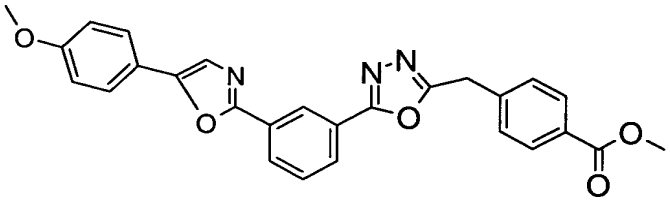
Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-yl)-benzoic acid



Using the procedure from Example B2 below and 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-yl)-benzoic acid methyl ester from Example B1a as starting material 0.09g (45%) desired product was obtained. MS: m/z (APCI, AP+) 440 $[M^-]^+$. NMR: DMSO ^1H δ (ppm) 3.81 (3H, s); 7.07-7.09 (2H, m); 7.68- 7.83 (5H, m); 8.15-8.17 (2H, m); 8.25- 8.33 (4H, m); 8.71-8.72 (1H, m).

EXAMPLE B2a

Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-ylmethyl)-benzoic acid methyl ester



0.24 g (0.49 mmol) of 4-[2-(N'-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoyl}-hydrazino)-2-oxo- ethyl]-benzoic acid methyl ester from Preparation 8 was dissolved in about 10 mL of poly phosphoric acid. The mixture was stirred at

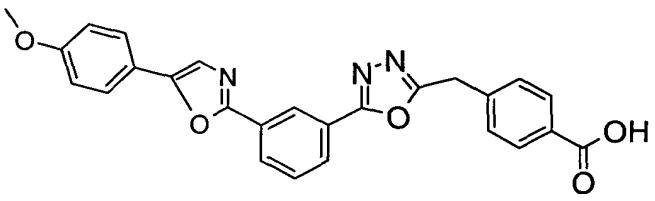
90-100 °C for 1 hour before allowing to cool to room temperature. Water was added and the product was extracted with 1:1:1 EtOAC/ THF/ Et_2O (2x). The extracts were combined and washed with saturated aqueous NaCl solution then dried $MgSO_4$. Slurried solid product in hot EtOAc and filtered. Dried in vacuum oven overnight at 70 °C to obtain 0.13 g (57%) desired product.

MS: m/z (APCI, AP+) 468 $[M^{\cdot}]^+$

NMR: DMSO ^1H δ (ppm) 3.80 (3H, s); 3.3.83 (3H, s); 7.04-7.07 (2H, m); 7.54-7.56 (2H, m); 7.57-7.79 (4H,m);7.91-7.96 (2H, m); 8.05-8.08 (1H, m); 8.25-8.27 (1H, m); 8.52-8.53 (1H, M).

EXAMPLE B2

Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-ylmethyl)-benzoic acid



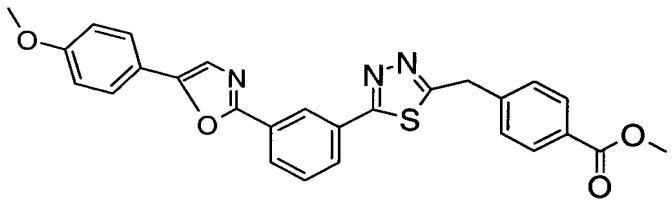
A solution of 0.25g (0.53mmol) 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-ylmethyl)-benzoic acid methyl ester from Example B2a in a 5:2:1 mixture of THF/ methanol/ water was added 1.0mL (1.0 mmol) 1N NaOH. The mixture was stirred 14 hours at room temperature before concentrating on a rotary evaporator. Partitioned between ether and water. Separated layers and acidified aqueous layer with 6M HCl. Extracted aqueous layer with 1:1 Et_2O/ EtOAc (2x), combined organic layers and wash with saturated aqueous NaCl solution and dried ($MgSO_4$). Obtained a solid from MeOH. Filter and dry in a vacuum oven overnight at room temperature to provide 0.068 g (28%) desired product.

MS: m/z (APCI, AP+) 454 $[M^{\cdot}]^+$

NMR: DMSO ^{1}H δ (ppm) 3.81 (3H, s); 4.49 (2H, S); 7.04-7.08 (2H, m); 7.72- 7.79 (3H, m); 7.88-7.99 (2H, m); 8.05- 8.08 (1H, m); 8.22 - 8.28 (1H m); 8.53- 8.54 (1H, m).

EXAMPLE B3a

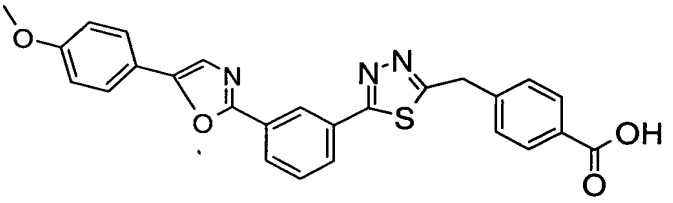
Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid methyl ester



To a suspension of 0.25 g (0.51 mmol) 4-[2-(N'-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-benzoyl}-hydrazino)-2-oxo- ethyl]-benzoic acid methyl ester from Preparation 8 in 10 mL dry dioxane was added P_2S_5 in one portion. The resulting mixture was warmed to 50 °C for 1 hour before cooling to room temperature and adding about 20 mL water. Stirred 2 hours and then filtered off solid product. Triturated in hot MeOH and filtered. Dissolved in THF and filtered through a plug of flash silica gel with THF eluent. Concentration gave 0.18g (73%) desired product. Used directly in the procedure of Example B3 without characterization.

EXAMPLE B3

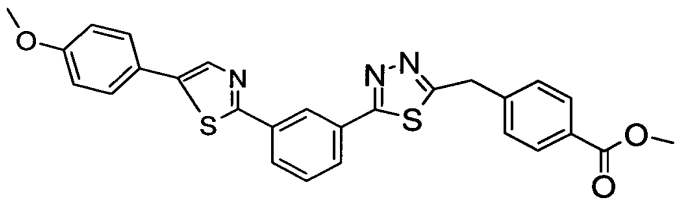
Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid



Using the procedure from Example B2 and 0.18g (0.37 mmol) 4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid methyl ester from Example B3a as starting material 0.079g (46%) desired product was obtained. MS: m/z (APCI, AP+) 470 $[M^{\cdot}]^{+}$. NMR: DMSO ^{1}H δ (ppm) 3.79 (3H, s); 4.63 (2H, s); 7.05-7.08 (2H, m); 7.50- 7.52 (2H, m); 7.67-7.79 (4H,M); 7.81-8.02 (2H,m); 8.02-8.04 (2H, m); 8.17-8.19 (1H, m); 8.20- 8.21 (1H, m); 8.52-8.53 (1H, m).

EXAMPLE B4a

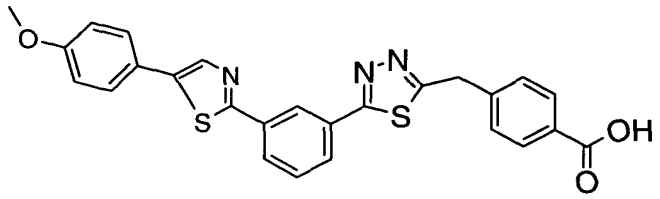
Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid methyl ester



Using the procedure from Example B3a and 0.33 (0.65 mmol) 4-[2-(N'-{3-[5-(4-methoxy-phenyl)-thiazol-2-yl]-benzoyl}-hydrazino)-2-oxo-ethyl]-benzoic acid methyl ester from Preparation 14 as starting material 0.18g (55%) desired product was obtained. MS: m/z (APCI, AP+) 500 $[M^{\cdot}]^{+}$ NMR: DMSO ^{1}H δ (ppm) 3.79 (3H, S); 3.83 (3H, s); 4.64 (2H, s); 7.01-7.03 (2H, m); 7.37- 7.67 (5H, m); 7.91-8.22 (4H, m); 8.23 (1H, s); 8.43-8.44 (1H, m).

EXAMPLE B4

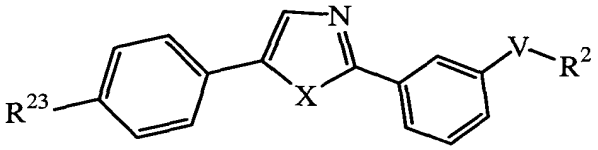
Synthesis of 4-(5-{3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid

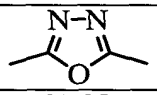
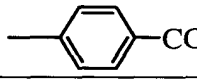
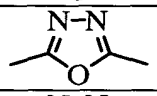
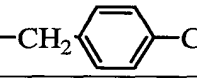
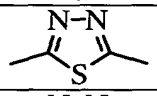
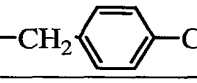
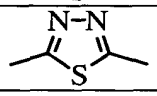
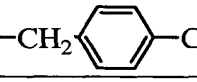


Using the procedure from Example B3 and 0.16g (0.32 mmol) 4-(5-{3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid methyl ester from Example B4a 0.023g (16%) desired product was obtained. MS: m/z (APCI, AP-) 487 $[M^-]^-$. NMR: DMSO ^1H δ (ppm) 3.79 (3H, S); 4.62 (2H, s); 7.01-7.03 (2H, m); 7.45- 7.88 (5H, m); 7.90-8.22 (4H, m); 8.24 (1H, s); 8.43-8.44 (1H, m).

The compounds of Example Table B beow were prepared according to the methods illustrated above in Schemes 6 to 10 and the preparations and procedures.

Example Table B.



Example No.	R^{23}	X	V	R^2	Characterizing Data
B1	CH_3O	O			See above
B2	CH_3O	O			See above
B3	CH_3O	O			See above
B4	CH_3O	S			See above

The compounds of Example Table B have the following chemical names (Example No.):

4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-yl)-benzoic acid (B1);

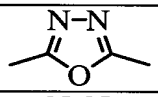
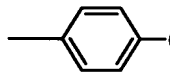
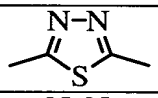
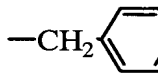
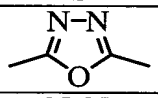
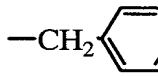
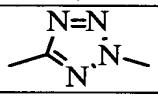
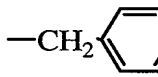
4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]oxadiazol-2-ylmethyl)-benzoic acid (B2);

4-(5-{3-[5-(4-Methoxy-phenyl)-oxazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid (B3); and

4-(5-{3-[5-(4-Methoxy-phenyl)-thiazol-2-yl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid (B4).

The compounds of Example Table C below were prepared according to the methods illustrated above in Schemes 6 to 10 or Schemes 1 to 5.

Example Table C.

Example No.	R^{23}	V	R^2	Characterizing Data
C1	H			MS: m/z (APCI, AP+) 381 $[M^{\cdot}]^+$
C2	F			MS: m/z (APCI, AP+) 429 $[M^{\cdot}]^+$
C3	H			MS: m/z (APCI, AP+) 395 $[M^{\cdot}]^+$
C4	F			Mp 210-212°C

The compounds of Example Table C have the following chemical names (Example No.):

4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-[1,3,4]oxadiazol-2-yl}-benzoic acid (C1);

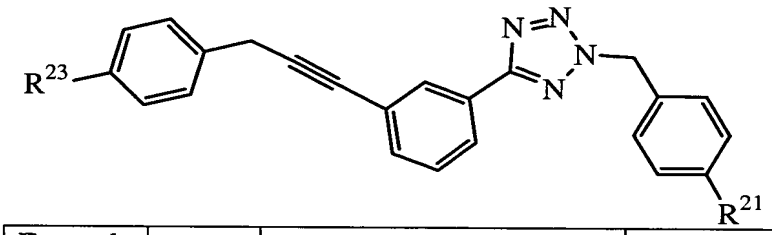
4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-[1,3,4]thiadiazol-2-ylmethyl)-benzoic acid (C2);

4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-[1,3,4]oxadiazol-2-ylmethyl}-benzoic acid (C3); and

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid (C4).

The compounds of Example Table D were prepared as described below.

Example Table D.



Example No.	R^{23}	R^{21}	Characterizing Data
D1	F	SO_3H	See below
D2	F	PO_3H_2	See below
D3	F	OCH_2COOH	See below
D4	H	$S(O)_2NH_2$	Mp 158-159°C
D5	F	$S(O)_2CH_3$	Mp 101-104°C
D6	H	CH_2NH_2	1H NMR (400 MHz, DMSO-D) d ppm 8.08(s, br, 2H), 8.00 (m, 2H), 7.56 (m, 2H), 7.46 (s, 4H), 7.37 (m, 4H), 7.25 (m, 1H), 6.00 (s, 2H), 4.01 (s, 2H), 3.91 (s, 2H)
D7	H	$CH_2N(H)C(O)(CH_2)_2CH_3$	1H NMR (400 MHz, DMSO-D) d ppm 8.25 (t, br, 1H), 8.00 (m, 2H), 7.55 (m, 2H), 7.37 (m, 6H), 7.24 (m, 3H), 5.94 (s, 2H), 4.22 (d, 2H), 3.91 (s, 2H), 2.07 (t, 2H), 1.50 (m, 2H), 0.82 (t, 3H).
D8	H	$CH_2N(H)C(O)CH_3$	1H NMR (400 MHz, DMSO-D) d ppm 8.29 (t, br, 1H), 8.00 (m, 2H), 7.55 (m, 2H), 7.37 (m, 6H), 7.24 (m, 3H), 5.94 (s, 2H), 4.20 (d, 2H), 3.91 (s, 2H), 1.82 (s, 3H).

EXAMPLE D1

Synthesis of 4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzenesulfonic acid

Step (a): 5-(3-bromophenyl)-2H-tetrazole

A mixture of 3-bromobenzonitrile (30.00g, 164.8mmol) in toluene (300mL) was treated with triethylamine hydrochloride (68.05g, 494.4mmol) and sodium azide (32.14g, 494.4mmol) and the reaction mixture heated to reflux over night. Cooled to room temperature, diluted with water (300mL), the layers were separated, and the aqueous portion acidified to pH 1 using concentrated HCl. The precipitated solid was collected by filtration, washed with water, and dried to give 34.96g of product (94.3% yield).

NMR (DMSO-d_6); 9.19-8.18 (m, 1H), 8.04-8.02 (dd, 1H), 7.79-7.76 (m, 1H), 7.57-7.53 (t, 1H)

MS (APCI) M+1 = 224.9

Mp 151.0-152.0°C

Step (b): 4-[5-(3-bromophenyl)tetrazol-2-ylmethyl]benzenesulfonic acid, sodium salt

A solution of 5-(3-bromophenyl)-2H-tetrazole (0.8g, 3.55mmol) in DMF (15mL) was treated with triethylamine (0.6mL, 4.25mmol) and the reaction mixture stirred at room temperature for 30 minutes. To this was added sodium 4-bromomethylbenzenesulfonate (1.17g, 4.27mmol) and the reaction mixture stirred over night at room temperature. The reaction mixture was evaporated to dryness, treated with acetic acid, and evaporated to dryness again. The white solid was triturated with ethyl acetate/methanol 4:1, the solid was collected by filtration, washed with ethyl acetate/methanol 4:1, and dried under house vacuum to afford 1.10g of white solid (78.3% yield).

NMR (DMSO-d_6); 8.14 (m, 1H), 8.04-8.01 (d, 1H), 7.74-7.71 (m, 1H), 7.62-7.60 (d, 2H), 7.51-7.48 (t, 1H), 7.36-7.34 (d, 2H), 5.99 (s, 2H)

MS (APCI) M-1 = 395.0

mp. >250.0°C

Step (c): 4-(5-{3-[3-(4-fluorophenyl)prop-1-ynyl]phenyl}tetrazol-2-ylmethyl)benzene-sulfonic acid

A suspension of 4-[5-(3-bromophenyl) tetrazol-2-ylmethyl]benzenesulfonic acid, sodium salt (0.50g, 1.27mmol) in DMF (3mL) was treated with diisopropylethylamine (0.88mL, 5.1mmol), palladium tetrakis(triphenylphosphine) ("$Pd(PPh_3)_4$", 0.29g, 0.25mmol), CuI (cat), and 1-fluoro-4-prop-2-ynyl-benzene (0.42g, 3.1mmol), and the mixture degassed with

nitrogen. The reaction mixture was heated in the microwave for 15 minutes at 100°C, cooled to room temperature, poured into 1N HCl, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and evaporated onto silica gel. The mesh was purified on a 3.5X15 cm silica gel column eluted with ethyl acetate ("EtOAc")-methanol ("MeOH") 4:1 with 1% acetic acid ("AcOH"). Evaporation and trituration with ether afforded 0.052g of orange solid (8.26% yield)

NMR (DMSO-d_6); 8.03-7.99 (m, 1H), 7.61-7.51 (m, 6H), 7.46-7.42 (dd, 1H), 7.36-7.33 (d, 2H), 7.19-7.15 (t, 2H), 5.98 (s, 2H), 3.90 (s, 2H)

MS (APCI) small M+1 = 449.0

EXAMPLE D2

Synthesis of [4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-phenyl]-phosphonic acid

Step (a): {4-[5-(3-bromophenyl) tetrazol-2-ylmethyl]benzyl}phosphonic acid dimethyl ester

To a solution of 5-(3-bromophenyl)-2H-tetrazole (0.5g, 2.22mmol) in DMF (15mL) was added cesium carbonate (0.94g, 2.89) and the mixture stirred at room temperature for 15 minutes. To this was added (4-bromo-methylbenzyl) phosphonic acid dimethyl ester (0.85g, 3.05mmol) and the reaction mixture stirred over night at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, filtered, and the evaporated to dryness.

The light yellow oil was dissolved in chloroform and evaporated onto silica gel. The silica gel mesh was purified on a 3.5X15 cm silica gel column eluted with ethyl acetate/methanol 9:1. Evaporation of the appropriate fractions followed by drying, afforded 0.85g of gummy oil (90.4% yield). The light yellow oil was purified again on a 5X15 cm silica gel column eluted with ethyl acetate. Drying afforded 0.64g of colorless oil.

NMR ($CDCl_3$); 8.28-8.27 (m, 1H), 8.07-8.05 (dd, 1H), 7.58-7.56 (m, 1H), 7.38-7.30 (m, 6H), 5.77 (s, 2H), 3.68 (s, 3H), 3.66 (s, 3H)

MS (APCI) no M+1 peak

Step (b): [4-(5-{3-[3-(4-fluorophenyl) prop-1-ynyl]phenyl}tetrazol-2-ylmethyl)benzyl]-phosphonic acid dimethyl ester

This reaction was carried out as described in Example D1, Step (c) using {4-[5-(3-bromophenyl) tetrazol-2-ylmethyl]benzyl}phosphonic acid dimethyl ester (0.61g, 1.33mmol) in place of 4-[5-(3-bromophenyl)tetrazol-2-ylmethyl]benzenesulfonic acid, sodium salt. This afforded 0.27g of yellow oil (42.6% yield).

NMR ($CDCl_3$); 8.21 (s, 1H), 8.07-8.04 (dd, 1H), 7.67-7.64 (m, 1H), 7.42-7.29 (m, 8H), 7.05-7.00 (t, 1H), 5.77 (s, 2H), 3.80 (s, 2H), 3.68 (s, 3H), 3.65 (s, 3H)

MS (APCI) no M+1 or M-1 peak

Step (c): [4-(5-{3-[3-(4-fluorophenyl) prop-1-ynyl]phenyl}tetrazol-2-ylmethyl)benzyl]-phosphonic acid

A solution of [4-(5-{3-[3-(4-fluorophenyl) prop-1-ynyl]phenyl}tetrazol-2-ylmethyl)benzyl] phosphonic acid dimethyl ester (0.25g, 0.53mmol) in methylene chloride (15mL) was cooled to 0°C, then treated with trimethylsilyliodide (0.23mL, 1.33mmol). The reaction mixture was removed from the cooling bath and stirred at room temperature for 1 hour. The reaction mixture was concentrated on the rotary evaporator without heat and the residue was treated with chloroform. The resulting solid was collected by filtration, washed with chloroform, triturated with hot ether, collected by filtration and dried. High performance liquid chromatography ("HPLC") indicates that this solid is 65% pure.

The solid was heated in hexanes/ethyl acetate 1:1, cooled to room temperature, collected by filtration and dried. The impure solid was washed with a small amount of methanol, collected, washed with methanol and dried. This afforded 0.0766g of yellow solid.

NMR (DMSO-d_6); 8.03-7.98 (m, 2H), 7.59-7.51 (m, 2H), 7.46-7.42 (m, 2H), 7.33-7.31 (d, 2H), 7.26-7.24 (m, 2H), 7.19-7.15 (m,2H), 5.93 (s, 2H), 3.90 (s, 2H), 2.96-2.90 (d, 2H)

MS (APCI) M+1 = 463.1

EXAMPLE D3

Synthesis of [4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-phenoxy]-acetic acid

Step (a): {4-[5-(3-bromophenyl) tetrazol-2ylmethyl]phenoxy}acetic acid tert-butyl ester

This reaction was carried out as described in Example D2, Step (a) using 5-(3-bromophenyl)-2H-tetrazole (0.87g, 2.89mmol) and (4-bromomethylphenoxy) acetic acid tert-butyl ester (0.50g, 2.22mmol) in place of (4-bromo-methylbenzyl) phosphonic acid dimethyl ester. This afforded 0.85g of light oil (84.6% yield)

NMR ($CDCl_3$); 8.28 (s, 1H), 8.07-8.05 (d, 1H), 7.58-7.55 (d, 1H), 7.38-7.31 (m, 3H), 6.90-6.88 (d, 2H), 5.72 (s, 2H), 4.50 (s, 2H), 1.48 (s, 9H)

MS (APCI) M+1 = 445.0

Step 2: [4-(5-{3-[3-(4-fluorophenyl)prop-1-ynyl]phenyl}tetrazol-2-ylmethyl)phenoxy]acetic acid tert-butyl ester

This reaction was carried out as described in Example D1, Step (c) using 1-fluoro-4-prop-2-ynyl-benzene (0.23g, 1.7mmol) and {4-[5-(3-bromophenyl) tetrazol-2ylmethyl]phenoxy}acetic acid tert-butyl ester (0.30g, 0.67mmol) in place of 4-[5-(3-bromophenyl)tetrazol-2-ylmethyl]-benzenesulfonic acid, sodium salt. This afforded 0.23g of the product (68.5% yield).

NMR ($CDCl_3$); 8.21 (s, 1H), 8.07-8.05 (d, 1H) 7.52-7.49 (m, 1H), 7.42-7.35 (m, 4H), 7.05-6.90 (t, 2H), 6.89-6.87 (d, 3H), 5.72 (s, 2H), 4.49 (s, 2H), 3.81 (s, 2H), 1.48 (s, 9H)

MS (APCI) M+1 (- t-Bu) = 443.1

Step 3: [4-(5-{3-[3-(4-fluorophenyl)prop-1-ynyl]phenyl}tetrazol-2-ylmethyl)phenoxy]acetic acid

A solution of [4-(5-{3-[3-(4-fluorophenyl)prop-1-ynyl]phenyl}tetrazol-2-ylmethyl) phenoxy]-acetic acid tert-butyl ester (0.19g. 0.38mmol) in trifluoroacetic acid ("TFA") (6mL) was stirred at room temperature for 75 minutes, then evaporated to dryness. The residue was triturated with ether, evaporated, triturated again with ether/hexanes, evaporated, then triturated with hexanes/ethyl acetate 3:1. The solid was collected by filtration, washed with hexanes/ethyl acetate 3:1 and dried to give 0.1047g of orange solid (59.11% yield).

NMR (DMSO-d_6) 12.99 (bs, 1H), 8.02-7.98 (m, 2H), 7.56-7.51 (m, 2H), 7.46-7.42 (m, 2H), 7.37-7.36 (d, 2H), 7.19-7.17 (t, 2H), 6.92-6.90 (d, 2H), 5.89 (s, 2H), 4.64 (bs, 2H), 3.90 (s, 2H)

MS (APCI) M-1 = 441.0

mp 158.2-159.6°C

Certain compounds of Example Table D have the following chemical names (Example No.):

4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzenesulfonamide (D4);

5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-2-(4-methanesulfonyl-benzyl)-2H-tetrazole (D5);

4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzylamine (D6);

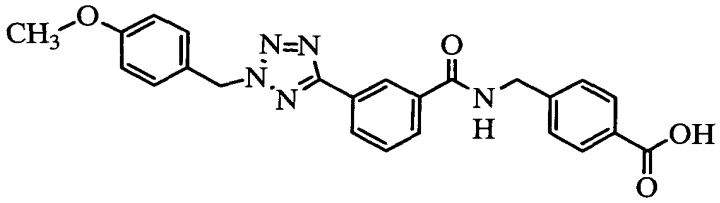
N-(4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzyl)-butyramide (D7); and

N-(4-{5-[3-(3-Phenyl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzyl)-acetamide (D8).

The compound of Example E1 was prepared by adapting the methods described above.

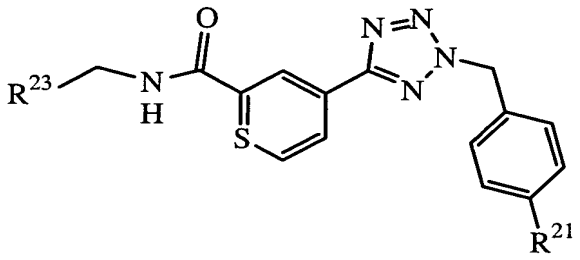
EXAMPLE E1

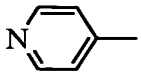
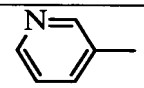
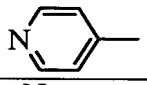
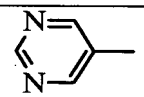
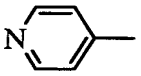
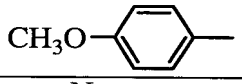
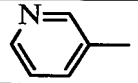
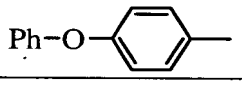
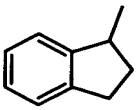
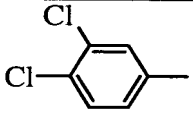
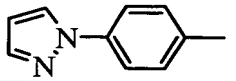
4-({3-[2-(4-Methoxy-benzyl)-2H-tetrazol-5-yl]-benzoylamino}-methyl)-benzoic acid trifluoroacetic acid salt (mp 202-205°C)



Additional compounds of this invention were prepared by adapting the methods described above and are shown below in Example Table F.

Example Table F.



Example No.	R^{23}	S	R^{21}	Characterizing Data
F1[1]		CH	COOH	Mp 222°C (dec)
F2[1]		CH	COOH	Mp 253°C (dec)
F3		N	$S(O)_2CH_3$	Mp 143-144°C
F4		N	$S(O)_2CH_3$	Mp 178-179°C
F5		N	-C≡N	Mp 178-179°
F6		N	$S(O)_2CH_3$	Mp 145-146°C
F7		N	$S(O)_2CH_3$	Mp 174-175°C
F8		N	$S(O)_2CH_3$	Mp 100-103°C
F9		N	$S(O)_2CH_3$	Mp 147-150°C
F10		N	$S(O)_2CH_3$	Mp 150-152°C
F11		N	$S(O)_2CH_3$	Mp 173-174°C
F12		N	COOH	Mp 193-194°C

(1) trifluoroacetic acid salt

The compounds of Example Table F have the following chemical names (Example No.):

4-(5-{3-[(Pyridin-4-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid; compound with trifluoro-acetic acid (F1);

4-(5-{3-[(Pyridin-3-ylmethyl)-carbamoyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid; compound with trifluoro-acetic acid (F2);

4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (F3);

4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid (pyrimidin-5-ylmethyl)-amide (F4);

4-[2-(4-Cyano-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (F5);

4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid 4-methoxy-benzylamide (F6);

4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid (pyridin-3-ylmethyl)-amide (F7);

4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid 4-phenoxy-benzylamide (F8);

4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid indan-1-ylamide (F9);

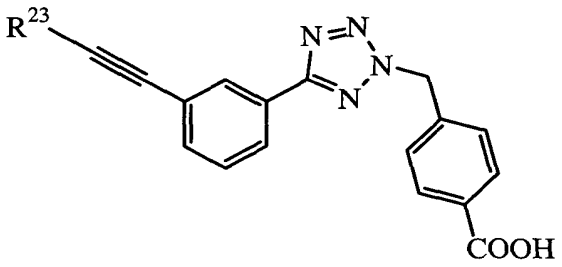
4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid 3,4-dichloro-benzylamide (F10);

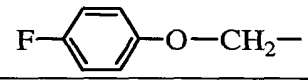
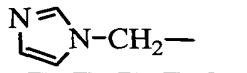
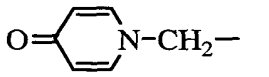
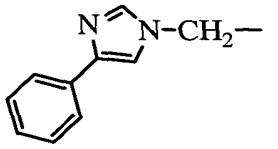
4-[2-(4-Methanesulfonyl-benzyl)-2H-tetrazol-5-yl]-pyridine-2-carboxylic acid 4-pyrazol-1-yl-benzylamide (F11); and

4-{5-[2-(4-Fluoro-benzylcarbamoyl)-pyridin-4-yl]-tetrazol-2-ylmethyl}-benzoic acid (F12).

Additional compounds of this invention were prepared by adapting the methods described above and are shown below in Example Table G.

Example Table G.



Example No.	R^{23}	Characterizing Data
G1	Ph	MP 226-228°C
G2	Ph-CH_2CH_2-	MP 198-199°C
G3	$(CH_3)_2CHCH_2$-	MP 192-193°C
G4		1H NMR (400 MHz, CHLOROFORM-D) d ppm 4.8 (s, 2 H) 5.8 (s, 2 H) 6.9 (m, 4 H) 7.4 (m, 4 H) 8.0 (m, 3 H) 8.1 (s, 1 H)
G5		1H NMR (400 MHz, DMSO-D6) d ppm 5.4 (s, 2 H) 6.1 (s, 2 H) 7.5 (d, J=8.5 Hz, 2 H) 7.6 (t, J=7.7 Hz, 1 H) 7.7 (dt, J=1.5 Hz, 2 H) 7.9 (s, 1 H) 7.9 (d, J=8.3 Hz, 2 H) 8.1 (m, 2 H) 9.2 (s, 1 H)
G6		1H NMR (400 MHz, CHLOROFORM-D) d ppm 5.0 (s, 2 H) 5.8 (s, 2 H) 6.9 (d, J=7.1 Hz, 2 H) 7.4 (m, 4 H) 7.9 (dd, J=7.9 Hz, 6 H) 8.0 (d, J=7.6 Hz, 1 H) 8.1 (s, 1 H)
G7		1H NMR (400 MHz, CHLOROFORM-D) d ppm 5.1 (s, 2 H) 5.7 (s, 2 H) 7.2 (s, 1 H) 7.2 (d, J=7.3 Hz, 1 H) 7.3 (m, 4 H) 7.4 (d, J=7.8 Hz, 2 H) 7.6 (s, 2 H) 7.9 (d, J=8.1 Hz, 2 H) 8.0 (d, J=7.8 Hz, 1 H) 8.1 (s, 1 H) 8.5 (s, 1 H)
G8	Ph-$C(CH_3)H$-	

The compounds of Example Table G have the following chemical names (Example No.):

4-[5-(3-Phenylethynyl-phenyl)-tetrazol-2-ylmethyl]-benzoic acid (G1);

4-{5-[3-(4-Phenyl-but-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid (G2);

4-{5-[3-(4-Methyl-pent-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid (G3);

4-(5-{3-[3-(4-Fluoro-phenoxy)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid (G4);

4-{5-[3-(3-Imidazol-1-yl-prop-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid (G5);

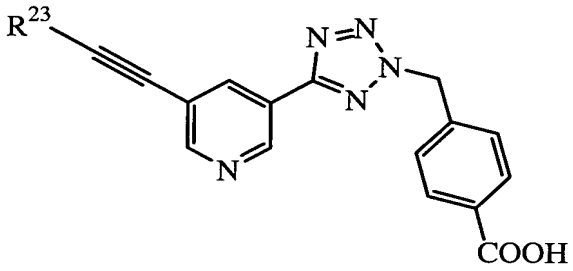
4-(5-{3-[3-(4-Oxo-4H-pyridin-1-yl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid (G6);

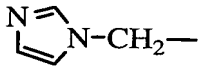
4-(5-{3-[3-(4-Phenyl-imidazol-1-yl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid (G7); and

4-{5-[3-(3-Phenyl-but-1-ynyl)-phenyl]-tetrazol-2-ylmethyl}-benzoic acid (G8).

Additional compounds of this invention were prepared by adapting the methods described above and are shown below in Example Table G.

Example Table H.



Example No.	R^{23}	Characterizing Data
H1	Ph-CH_2-	MP 211-213°C
H2	4-fluoro-benzyl	See below
H3		1H NMR (400 MHz, DMSO-D6) d ppm 5.5 (s, 2 H) 6.1 (s, 2 H) 7.5 (d, J=8.1 Hz, 3 H) 7.9 (d, J=7.6 Hz, 3 H) 8.5 (s, 1 H) 8.9 (s, 1 H) 9.2 (s, 2 H)
H4	4-methoxy-benzyl	1H NMR (400 MHz, CHLOROFORM-D) d ppm 3.8 (s, 2 H) 3.8 (s, 3 H) 5.8 (s, 2 H) 6.9 (d, J=8.5 Hz, 2 H) 7.3 (s, 1 H) 7.3 (d, J=8.8 Hz, 2 H) 7.4 (d, J=8.1 Hz, 2 H) 8.1 (d, J=8.1 Hz, 2 H) 8.4 (d, J=1.7 Hz, 1 H) 8.7 (s, 1 H) 9.2 (s, 1 H)

The compounds of Example Table H have the following chemical names (Example No.):

4-{5-[5-(3-Phenyl-prop-1-ynyl)-pyridin-3-yl]-tetrazol-2-ylmethyl}-benzoic acid (H1);

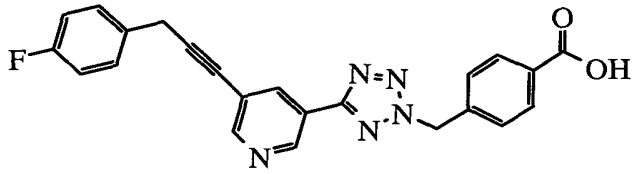
4-(5-{5-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-pyridin-3-yl}-tetrazol-2-ylmethyl)-benzoic acid (H2);

4-{5-[5-(3-Imidazol-1-yl-prop-1-ynyl)-pyridin-3-yl]-tetrazol-2-ylmethyl}-benzoic acid (H3); and

4-(5-{5-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-pyridin-3-yl}-tetrazol-2-ylmethyl)-benzoic acid (H4).

The compound of Example H2 in Table H above was synthesized according to the procedure described below.

EXAMPLE H2



4-(5-{5-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-pyridin-3-yl}-tetrazol-2-ylmethyl)-benzoic acid

Step (a): 3-Bromo-5-(2H-tetrazol-5-yl)-pyridine.

5-Bromo-nicotinonitrile (10.0 g, 55 mmol) was converted to the corresponding tetrazole (10.8 g, 75%) using the reaction conditions previously described in Step (a) of Example 1. ^{1}HNMR (DMSO-d6) δ 9.17 (s, 1H), 8.89 (2, 1H), 8.59 (s, 1H).

Step (b): 4-[5-(5-Bromo-pyridin-3-yl)-tetrazol-2-ylmethyl]-benzoic acid tert-butyl ester

The tetrazole (27.3 g, 104 mmol) from Step (a) was treated with 4-bromomethyl-benzoic acid tert-butyl ester (31.0 g, 114 mmol) and cesium carbonate (74.3 g, 228 mmol) in dimethylformamide (400 mL) at room temperature for 5.5 hours. The solvent was evaporated in vacuo and the residue passed through a pad of silica gel eluting with CH_2Cl_2:THF 19:1, to give a 9:1 mixture of regioisomers (40.07 g, 93%). ^{1}HNMR (DMSO-d6) δ 9.16 (s, 1H), 8.87

(s, 1H), 8.54 (s, 1H), 7.91 (d, J=8 Hz, 2H), 7.51 (d, J=9 Hz, 2H), 6.13 (s, 2H), 1.57 (s, 9H).

Step (c) 4-(5-{5-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-pyridin-3-yl}-tetrazol-2-ylmethyl)-benzoic acid tert-butyl ester

The product of Step (b) (300 mg, 0.72 mmol) was mixed with 3-(4-(fluorophenyl)-1-propyne (126 mg, 0.94 mmol), diisopropylamine, (0.51mL, 2.9 mmol) in dimethylformamide (5 mL). The solution was degassed. Tetrakis-triphenylphosphine palladium (0) (166 mg, 0.14 mmol), and cuprous iodide (27 mg, 0.14 mmol) were added and the mixture microwaved at 120°C for 1200 seconds. The DMF was removed in vacuo. The crude product was purified by silica gel chromatography, eluting with dichloromethane:THF 49:1 (124 mg, 37%).

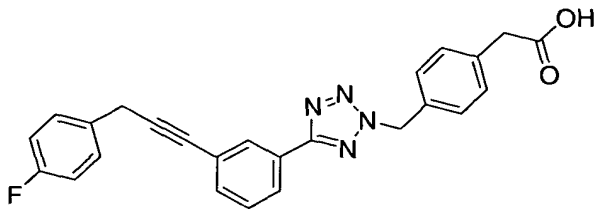
^{1}HNMR (DMSO-d6) δ 9.12 (s, 1H), 8.78 (s, 1H), 8.36 (s, 1H), 7.89 (d, J=8 Hz, 2H), 7.50 (d, J=9 Hz, 2H), 7.45 (m, 2H), 7.17 (m, 2H), 6.12 (s, 2H), 3.95 (s, 2H), 1.50 (s, 9H).

Step (d) 4-(5-{5-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-pyridin-3-yl}-tetrazol-2-ylmethyl)-benzoic acid

The product of Step (c) was treated with trifluoroacetic acid in dichloromethane in a manner analogous to that described above in Step (c) of Example 43, then rotary evaporated in vacuo. Trituration of the resulting oil with diethyl ether gave the title product (84 mg, 78%). ^{1}HNMR (DMSO-d6) δ 13.0 (s, 1H), 9.13 (s, 1H), 8.78 (s, 1H), 8.36 (s, 1H), 7.93 (d, J=8 Hz, 2H), 7.50 (d, J=8 Hz, 2H), 7.45 (m, 2H), 7.17 (m, 2H), 6.13 (s, 2H), 3.95 (s, 2H).

EXAMPLE I1

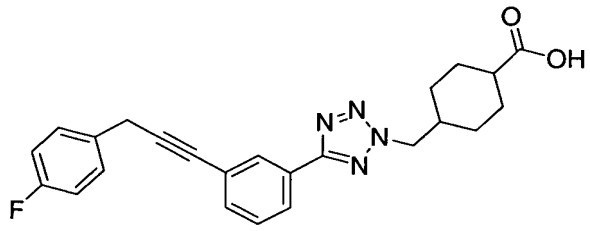
[4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-phenyl]-acetic acid



M.P. 158-159°C.

EXAMPLE I2

4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-cyclohexanecarboxylic acid

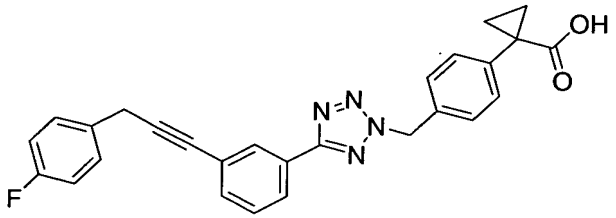


MP 172-173°C.

The following compounds of Examples K1 to K3 are compounds of Formula I that will be synthesized according to the procedures described above.

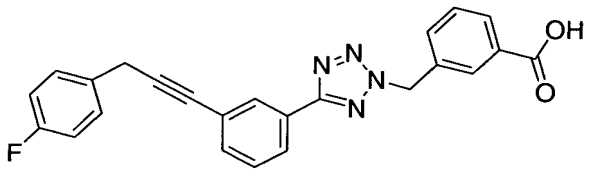
EXAMPLE K1

1-[4-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-phenyl]-cyclopropanecarboxylic acid



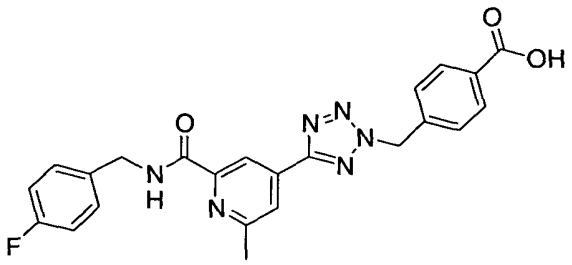
EXAMPLE K2

3-(5-{3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-phenyl}-tetrazol-2-ylmethyl)-benzoic acid



EXAMPLE K3

4-{5-[2-(4-Fluoro-benzylcarbamoyl)-6-methyl-pyridin-4-yl]-tetrazol-2-ylmethyl}-benzoic acid



The compounds of Formula I can be evaluated in standard assays for their ability to inhibit the catalytic activity of MMP enzymes. The assays used to evaluate the MMP biological activity of the invention compounds are well-known and routinely used by those skilled in the study of MMP inhibitors and their use to treat clinical conditions. For example, compounds of Formula I may be readily identified by assaying a test compound for inhibition of MMP-13 according to Biological Methods 1 or 2, and further assaying the test compound for allosteric inhibition of MMP-13 according to Biological Methods 3 or 4, as described below.

The compounds of Formula I, as illustrated by the compounds of Examples 1 to 37, have been shown to be potent inhibitors of MMP-13 catalytic domain. Potencies, as measured by IC_{50}'s, with MMP-13 catalytic domain for the invention compounds typically range from about 0.039 μM to about 46 μM. For example, the IC_{50} of the compound of Example 4 was measured at 0.039 μM and the IC_{50} of the compound of Example 2 was measured at 0.058 μM.

MMP-13 catalytic domain inhibition data for the compounds of Examples 1 to 37 are shown below in Biological Data Table 1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table 1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
1		2		3	

4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37					

MMP-13 catalytic domain inhibition for the compounds of Example Table A are shown below in Biological Table A1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table A1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
A1	0.44	A2	>3	A3	1.4
A4	0.4	A5	1.8	A6	1.0
A7	0.018	A8	1.3	A9	0.0036
A10	N/a				

N/a means not available

MMP-13 catalytic domain inhibition for the compounds of Example Table B are shown below in Biological Table B1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table B1.

Example No.	MMP-13CD	Example No.	MMP-13CD	Example No.	MMP-13CD

	IC_{50} (μM)		IC_{50} (μM)		IC_{50} (μM)
B1	49	B2	0.2	B3	0.014
B4	N/a	B5	N/a	B6	N/a

N/a means not available

MMP-13 catalytic domain inhibition for the compounds of Example Table C are shown below in Biological Table C1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table C1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
C1	3.4	C2	0.0011	C3	N/a
C4	0.0015				

N/a means not available

MMP-13 catalytic domain inhibition for the compounds of Example Table D are shown below in Biological Table D1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table D1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
D1	0.0045	D2	0.013	D3	0.007
D4	0.15	D5	0.15	D6	2.8
D7	1.3	D8	0.33		

MMP-13 catalytic domain inhibition for the compound of Example E1 is shown below in Biological Table E1 in the column labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table E1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
E1	0.058				

MMP-13 catalytic domain inhibition for the compounds of Example Table F are shown below in Biological Table F1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table F1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
F1	0.099	F2	0.28	F3	0.022
F4	0.21	F5	0.024	F6	0.024
F7	0.11	F8	0.19	F9	16
F10	0.047	F11	11	F12	0.0017

MMP-13 catalytic domain inhibition for the compounds of Example Table G are shown below in Biological Table G1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table G1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
G1	0.69	G2	0.28	G3	N/a
G4	0.086	G5	0.0068	G6	0.0064
G7	0.029	G8	1.8		

N/a means not available

MMP-13 catalytic domain inhibition for the compounds of Example Table H are shown below in Biological Table H1 in the columns labelled "MMP-13CD IC_{50} (μM)."

Biological Data Table H1.

Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)	Example No.	MMP-13CD IC_{50} (μM)
H1	0.010[1]	H2	0.0083	H3	0.16
H4	0.0027				

1) average of two data

The IC_{50} with MMP-13CD of the compound of Example I1 was 0.0026 μM. The IC_{50} with MMP-13CD of the compound of Example I2 was 0.0012 μM.

Invention compounds can be further screened with full-length MMP-2, full-length MMP-7, full-length MMP-9, and MMP-14 catalytic domain to determine selectivity of the inhibitors with MMP-13 versus the other MMP enzymes also. Selectivities of the invention compounds for MMP-13 catalytic domain versus another MMP enzyme (full-length or catalytic domain), as determined by dividing the IC_{50} for the inhibitor with a comparator MMP enzyme by the IC_{50} of the inhibitor with MMP-13 catalytic domain, are expected to range from 5 to 50,000 fold.

Certain compounds of Formula I have been assayed with MMP-1 full-length, MMP-3 catalytic domain, MMP-7 full-length, MMP-8 full-length, MMP-9 full-length, MMP-12 catalytic domain, MMP-14 catalytic domain, and MMP-17 catalytic domain. The IC_{50}'s for the compounds of Example Nos. ("Ex. No.") C2, C4, F12, and H4 are as shown below in Biological Table 1 in the columns labelled "MMP-3CD IC_{50} (μM)," "MMP-12CD IC_{50} (μM)," "MMP-14CD IC_{50} (μM)," and/or "MMP-17CD IC_{50} (μM)."

Biological Table 1.

Ex. No.	MMP-1FL IC_{50} (μM	MMP-3CD IC_{50} (μM)	MMP-7 IC_{50} (μM)	MMP-8FL IC_{50} (μM)	MMP-9FL IC_{50} (μM)	MMP-12CD IC_{50} (μM)	MMP-14CD IC_{50} (μM)	MMP-17CD IC_{50} (μM)
C2	>30	100	7.9	>100	>30	N/a[1]	27	>100
C4	N/a	4.7	N/a	>100	>100	18	>30	30

F12	>100	100	>100	>100	>100	N/a	>100	N/a
H4	>100	4.3	>30	>100	>30	N/a	>30	>100

To determine the inhibitory profiles, the compounds of Formula I have been evaluated in standard assays for their ability to inhibit the catalytic activity of various MMP enzymes. The assays used to evaluate the MMP biological activity of the invention compounds are well-known and routinely used by those skilled in the study of MMP inhibitors and their use to treat clinical conditions.

The assays measure the amount by which a test compound reduces the hydrolysis of a thiopeptolide substrate catalyzed by a matrix metalloproteinase enzyme. Such assays are described in detail by Ye et al., in Biochemistry, 1992;31(45):11231-11235, which is incorporated herein by reference. One such assay is described below in Biological Method 1.

Some of the particular methods described below use the catalytic domain of the MMP-13 enzyme, namely matrix metalloproteinase-13 catalytic domain ("MMP-13CD"), rather than the corresponding full-length enzyme, MMP-13. It has been shown previously by Ye Qi-Zhuang, Hupe D., and Johnson L. (*Current Medicinal Chemistry*, 1996;3:407-418) that inhibitor activity against a catalytic domain of an MMP is predictive of the inhibitor activity against the respective full-length MMP enzyme.

BIOLOGICAL METHOD 1

Thiopeptolide substrates show virtually no decomposition or hydrolysis at or below neutral pH in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt. A 100 μL assay mixture will contain 50 mM of N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffer ("HEPES," pH 7.0), 10 mM $CaCl_2$, 100 μM thiopeptolide substrate, and 1 mM 5,5'-dithio-bis-(2-nitro-benzoic acid) (DTNB). The thiopeptolide substrate concentration may be varied, for example from 10 to 800 μM to obtain K_m and K_{cat} values. The change in absorbance at 405 nm is monitored on a Thermo Max microplate reader

(molecular Devices, Menlo Park, CA) at room temperature (22°C). The calculation of the amount of hydrolysis of the thiopeptolide substrate is based on $E_{412} = 13600\ M^{-1}\ cm^{-1}$ for the DTNB-derived product 3-carboxy-4-nitrothiophenoxide. Assays are carried out with and without matrix metalloproteinase inhibitor compounds, and the amount of hydrolysis is compared for a determination of inhibitory activity of the test compounds.

Test compounds were evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of catalytic activity of the respective enzyme.

It should be appreciated that the assay buffer used with MMP-3CD was 50 mM N-morpholinoethane sulfonate ("MES") at pH 6.0 rather than the HEPES buffer at pH 7.0 described above.

The test described above for the inhibition of MMP-13 may also be adapted and used to determine the ability of the compounds of Formula I to inhibit the matrix metalloproteases MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

BIOLOGICAL METHOD 2

Some representative compounds of Formula I have been evaluated for their ability to inhibit MMP-13. Inhibitor activity versus other MMPs with the compounds may be determined using, for example, MMP-1FL, which refers to full length interstitial collagenase; MMP-2FL, which refers to full length Gelatinase A; MMP-3CD, which refers to the catalytic domain of stromelysin; MMP-7FL, which refers to full length matrilysin; MMP-9FL, which refers to full length Gelatinase B; MMP-13CD, which refers to the catalytic domain of collagenase 3; and MMP-14CD, which refers to the catalytic domain of MMP-14. Test compounds can be evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of the hydrolytic activity of the respective enzyme.

The results of the above assays with other MMPs will establish that the compounds of Formula I are potent inhibitors of MMP enzymes, and are especially useful due to their selective inhibition of MMP-13. Because of this potent and selective inhibitory activity, the compounds are especially useful to treat diseases mediated by the MMP enzymes.

Allosteric inhibitors of MMP-13 which are compounds of Formula I may be readily identified by assaying a test compound for inhibition of MMP-13 according to the methods described below in Biological Methods 3 and 4.

BIOLOGICAL METHOD 3

Fluorigenic peptide-1 substrate based assay for identifying compounds of Formula I as allosteric inhibitors of MMP-13:

Final assay conditions:

50 mM HEPES buffer (pH 7.0)

10 mM $CaCl_2$

10 μM fluorigenic peptide-1 ("FP1") substrate

0 or 15 mM acetohydroxamic acid (AcNHOH) = 1 K_d

2% DMSO (with or without inhibitor test compound)

0.5 nM MMP-13CD enzyme

Stock solutions:

1) 10X assay buffer: 500 mM HEPES buffer (pH 7.0) plus 100 mM $CaCl_2$
2) 10 mM FP1 substrate: (Mca)-Pro-Leu-Gly-Leu-(Dnp)-Dpa-Ala-Arg-NH_2 (Bachem, M-1895; "A novel coumarin-labeled peptide for sensitive continuous assays of the matrix metalloproteinases," Knight C.G., Willenbrock F., and Murphy, G., FEBS Lett., 1992;296:263-266). Is prepared 10 mM stock by dissolving 5 mg FP1 in 0.457 mL DMSO.
3) 3 M AcNHOH: Is prepared by adding 4 mL H_2O and 1 mL 10X assay buffer to 2.25 g AcNHOH (Aldrich 15,903-4). Adjusting pH to 7.0 with NaOH. Diluting volume to 10 mL with H_2O. Final solution will contain 3 M AcNHOH, 50 mM HEPES buffer (pH 7.0), and 10 mM $CaCl_2$.
4) AcNHOH dilution buffer: 50 mM HEPES buffer (pH 7.0) plus 10 mM $CaCl_2$

5) MMP-13CD enzyme: Stock concentration = 250 nM.

6) Enzyme dilution buffer: 50 mM HEPES buffer (pH 7.0), 10 mM $CaCl_2$, and 0.005% BRIJ 35 detergent (Calbiochem 203728; Protein Grade, 10%)

Procedure (for one 96-well microplate):

A. Prepared assay mixture:

1100 µL 10X assay buffer

11 µL 10 mM FP1

55 µL 3 M AcNHOH or 55 µL AcNHOH dilution buffer

8500 µL H_2O

B. Diluted MMP-13CD to 5 nM working stock:

22 µL MMP-13CD (250 nM)

1078 µL enzyme dilution buffer

C. Ran kinetic assay:

1. Dispense 2 µL inhibitor test sample (in 100% DMSO) into well.
2. Add 88 µL assay mixture and mix well, avoiding bubbles.
3. Initiate reactions with 10 µL of 5 nM MMP-13CD; mix well, avoid bubbles.
4. Immediately measure the kinetics of the reactions at room temperature.

Fluorimeter: F_{max} Fluorescence Microplate Reader & SOFTMAX PRO Version 1.1 software (Molecular Devices Corporation; Sunnyvale, CA 94089).

Protocol menu:

excitation: 320 nm	emission: 405 nm
run time: 15 min	interval: 29 sec
RFU min: -10	RFU max: 200
V_{max} points: 32/32	

D. Compared % of control activity and/or IC_{50} with inhibitor test compound ±AcNHOH.

Hydrolysis of the fluorigenic peptide-1 substrate, [(Mca)Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2; Bachem, catalog number M-1895], wherein "Mca" is (7-methoxy-coumarin-4-yl)acetyl and "Dpa" is (3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl), is used to screen for MMP-13 catalytic domain (CD)

inhibitors. (Dpa may also be abbreviated as "Dnp".) Reactions (100 μL) contain 0.05 M Hepes buffer (pH 7), 0.01 M calcium chloride, 0.005% polyoxyethylene (23) lauryl ether ("Brij 35"), 0 or 15 mM acetohydroxamic acid, 10 μM FP1, and 0.1 mM to 0.5 nM inhibitor in DMSO (2% final).

After recombinant human MMP-13CD (0.5 nM final) is added to initiate the reaction, the initial velocity of FP1 hydrolysis is determined by monitoring the increase in fluorescence at 405 nm (upon excitation at 320 nm) continuously for up to 30 minutes on a microplate reader at room temperature. Alternatively, an endpoint read can also be used to determine reaction velocity provided the initial fluorescence of the solution, as recorded before addition of enzyme, is subtracted from the final fluorescence of the reaction mixture. The inhibitor is assayed at different concentration values, such as, for example, 100 μM, 10 μM, 1 μM, 100 nM, 10 nM, and 1 nM. Then the inhibitor concentration is plotted on the X-axis against the percentage of control activity observed for inhibited experiments versus uninhibited experiments (i.e., (velocity with inhibitor) divided by (velocity without inhibitor) × 100) on the Y-axis to determine IC_{50} values. This determination is done for experiments done in the presence, and experiments done in the absence, of acetohydroxamic acid. Data are fit to the equation: percent control activity = $100/[1+(([I]/IC_{50})^{slope})]$, where [I] is the inhibitor concentration, IC_{50} is the concentration of inhibitor where the reaction rate is 50% inhibited relative to the control, and slope is the slope of the IC_{50} curve at the curve's inflection point, using nonlinear least-squares curve-fitting equation regression.

Results may be expressed as an IC_{50} Ratio (+/-) ratio, which means a ratio of the IC_{50} of the inhibitor with MMP-13 and an inhibitor to the catalytic zinc of MMP-13, divided by the IC_{50} of the inhibitor with MMP-13 without the inhibitor to the catalytic zinc of MMP-13. Compounds of Formula I which are allosteric inhibitors of MMP-13 are expected to have an IC_{50} Ratio (+/-) ratio of less than 1, and are expected to be synergistic with the inhibitor to the catalytic zinc of MMP-13 such as, for example, AcNHOH. Compounds of Formula I which are not allosteric inhibitors of MMP-13 will be inactive in the assay or will have an IC_{50}

Ratio (+/-) of greater than 1, unless otherwise indicated. Results can be confirmed by kinetics experiments which are well known in the biochemical art.

BIOLOGICAL METHOD 4

Fluorigenic peptide-1 based assay for identifying allosteric inhibitors of matrix metalloproteinase-13 catalytic domain ("MMP-13CD"):

In a manner similar to Biological Method 3, an assay is run wherein 1,10-phenanthouroline is substituted for acetohydroxamic acid to identify compounds of Formula I.

Animal models may be used to establish that the instant compounds of Formula I, or a pharmaceutically acceptable salt thereof, would be useful for preventing, treating, and inhibiting cartilage damage, and thus for treating osteoarthritis, for example. Examples of such animal models are described below in Biological Methods 5 and 6.

BIOLOGICAL METHOD 5

Monosodium Iodoacetate-induced Osteoarthritis in Rat Model of Cartilage Damage ("MIA Rat"):

One end result of the induction of osteoarthritis in this model, as determined by histologic analysis, is the development of an osteoarthritic condition within the affected joint, as characterized by the loss of Toluidine blue staining and formation of osteophytes. Associated with the histologic changes is a concentration-dependent degradation of joint cartilage, as evidenced by affects on hind-paw weight distribution of the limb containing the affected joint, the presence of increased amounts of proteoglycan or hydroxyproline in the joint upon biochemical analysis, or histopathological analysis of the osteoarthritic lesions.

Generally, In the MIA Rat model on Day 0, the hind-paw weight differential between the right arthritic joint and the left healthy joint of male Wistar rats (150 g) are determined with an incapacitance tester, model 2KG (Linton Instrumentation, Norfolk, United Kingdom). The incapacitance tester has a chamber on top with an outwardly sloping front wall that supports a rat's front

limbs, and two weight sensing pads, one for each hind paw, that facilitates this determination. Then the rats are anesthetized with isofluorine, and the right, hind leg knee joint is injected with 1.0 mg of mono-iodoacetate ("MIA") thorough the infrapatellar ligament. Injection of MIA into the joint results in the inhibition of glycolysis and eventual death of surrounding chondrocytes. The rats are further administered either an invention compound or vehicle (in the instant case, water) daily for 14 days or 28 days. The invention compound is typically administered at a dose of 30 mg per kilogram of rat per day (30 mg/kg/day), but the invention compound may be administered at other doses such as, for example, 10 mg/kg/day, 60 mg/kg/day, 90-mg/kg/day, or 100 mg/kg/day according to the requirements of the compound being studied. It is well within the level of ordinary skill in the pharmaceutical arts to determine a proper dosage of an invention compound in this model. Administration of the invention compound in this model is optionally by oral administration or intravenous administration via an osmotic pump. After 7 and 14 days for a two-week study, or 7, 14, and 28 days for a four-week study, the hind-paw weight distribution is again determined. Typically, the animals administered vehicle alone place greater weight on their unaffected left hind paw than on their right hind paw, while animals administered an invention compound show a more normal (i.e., more like a healthy animal) weight distribution between their hind paws. This change in weight distribution was proportional to the degree of joint cartilage damage. Percent inhibition of a change in hind paw joint function is calculated as the percent change in hind-paw weight distribution for treated animals versus control animals. For example, for a two week study,

Percent inhibition of a change in hind paw weight distribution

$$= \left\{ 1 - \left[\frac{(\Delta W_G)}{(\Delta W_C)} \right] \right\} \text{ X } 100$$

wherein: ΔW_C is the hind-paw weight differential between the healthy left limb and the arthritic limb of the control animal administered vehicle alone, as measured on Day 14; and

ΔW_G is the hind-paw weight differential between the healthy left limb and the arthritic limb of the animal administered an invention compound, as measured on Day 14.

In order to measure biochemical or histopathological end points in the MIA Rat model, some of the animals in the above study may be sacrificed, and the amounts of free proteoglycan in both the osteoarthritic right knee joint and the contralateral left knee joint may be determined by biochemical analysis. The amount of free proteoglycan in the contralateral left knee joint provides a baseline value for the amount of free proteoglycan in a healthy joint. The amount of proteoglycan in the osteoarthritic right knee joint in animals administered an invention compound, and the amount of proteoglycan in the osteoarthritic right knee joint in animals administered vehicle alone, are independently compared to the amount of proteoglycan in the contralateral left knee joint. The amounts of proteoglycan lost in the osteoarthritic right knee joints are expressed as percent loss of proteoglycan compared to the contralateral left knee joint control. The percent inhibition of proteoglycan loss, may be calculated as {[(proteoglycan loss from joint (%) with vehicle) - (proteoglycan loss from joint with an invention compound)] ÷ (proteoglycan loss from joint (%) with vehicle)} × 100.

The MIA Rat data that are expected from the analysis of proteoglycan loss would establish that an invention compound is effective for inhibiting cartilage damage and inflammation and/or alleviating pain in mammalian patients, including human.

The results of these studies with oral dosing may be presented in tabular format in the columns labelled "IJFL (%+/- SEM)", wherein IJFL means Inhibition of Joint Function Limitation, "SDCES", wherein SDCES means Significant Decrease In Cartilage Erosion Severity, and "SIJWHLE", wherein SIJWHLE means Significant Increase in Joints Without Hind Limb Erosion.

The proportion of subjects without hind limb erosions may be analyzed via an *Exact Sequential Cochouran-Armitage Trend* test (*SAS*® Institute, 1999). The Cochouran-Armitage Trend test is employed when one wishes to determine whether the proportion of positive or "Yes" responders increases or decreases

with increasing levels of treatment. For the particular study, it is expected that the number of animals without joint erosions increased with increasing dose.

The ridit analysis may be used to determine differences in overall erosion severity. This parameter takes into account both the erosion grade (0 = no erosion, I = erosion extending into the superficial or middle layers, or II = deep layer erosion), and area (small, medium and large, quantified by dividing the area of the largest erosion in each score into thirds) simultaneously. The analysis recognizes that each unit of severity is different, but does not assume a mathematical relationship between units.

Another animal model for measuring effects of an invention compound on cartilage damage and inflammation and/or pain is described below in Biological Method 6.

BIOLOGICAL METHOD 6

Induction of Experimental Osteoarthritis in Rabbit ("EOA in Rabbit"):

Normal rabbits are anaesthetized and anteromedial incisions of the right knees performed. The anterior cruciate ligaments are visualized and sectioned. The wounds are closed and the animals are housed in individual cages, exercised, and fed ad libitum. Rabbits are given either vehicle (water) or an invention compound dosed three times per day with 30-mg/kg/dose or 10-mg/kg/dose. The invention compound may be administered at other doses such as, for example, 3 times 20 mg/kg/day or 3 times 60 mg/kg/day according to the requirements of the invention compound being studied. The rabbits are euthanized 8 weeks after surgery and the proximal end of the tibia and the distal end of the femur are removed from each animal.

Macroscopic Grading

The cartilage changes on the femoral condyles and tibial plateaus are graded separately under a dissecting microscope (Stereozoom, Bausch & Lomb, Rochester, NY). The depth of erosion is graded on a scale of 0 to 4 as follows: grade 0 = normal surface; Grade 1 = minimal fibrillation or a slight yellowish discoloration of the surface; Grade 2 = erosion extending into superficial or

middle layers only; Grade 3 = erosion extending into deep layers; Grade 4 = erosion extending to subchondral bone. The surface area changes are measured and expressed in mm^2. Representative specimens may also be used for histologic grading (see below).

Histologic Grading

Histologic evaluation is performed on sagittal sections of cartilage from the lesional areas of the femoral condyle and tibial plateau. Serial sections (5 um) are prepared and stained with safranin-O. The severity of OA lesions is graded on a scale of 0 - 14 by two independent observers using the histologic-histochemical scale of Mankin *et al.* This scale evaluates the severity of OA lesions based on the loss of safranin-O staining (scale 0 - 4), cellular changes (scale 0 - 3), invasion of tidemark by blood vessels (scale 0 - 1) and structural changes (scale 0 - 6). On this latter scale, 0 indicates normal cartilage structure and 6 indicates erosion of the cartilage down to the subchondral bone. The scoring system is based on the most severe histologic changes in the multiple sections.

Representative specimens of synovial membrane from the medial and lateral knee compartments are dissected from underlying tissues. The specimens are fixed, embedded, and sectioned (5 um) as above, and stained with hematoxylin-eosin. For each compartment, two synovial membrane specimens are examined for scoring purposes and the highest score from each compartment is retained. The average score is calculated and considered as a unit for the whole knee. The severity of synovitis is graded on a scale of 0 to 10 by two independent observers, adding the scores of 3 histologic criteria: synovial lining cell hyperplasia (scale 0 - 2); villous hyperplasia (scale 0 - 3); and degree of cellular infiltration by mononuclear and polymorphonuclear cells (scale 0 - 5): 0 indicates normal structure.

Statistical Analysis

Mean values and SEM is calculated and statistical analysis was done using the Mann-Whitney U-test.

The results of these studies would be expected to show that an invention compound would reduce the size of the lesion on the tibial plateaus, and perhaps

the damage in the tibia or on the femoral condyles. In conclusion, these results would show that an invention compound would have significant inhibition effects on the damage to cartilage.

The foregoing studies would establish that an invention compound is effective for the inhibition of cartilage damage and inflammation and/or alleviating pain, and thus useful for the treatment of osteoarthritis or rheumatoid arthritis in human, and other mammalian disorders. Such a treatment offers a distinct advantage over existing treatments that only modify pain or inflammation or and other secondary symptoms. The effectiveness of an invention compound in this model would indicate that the invention compound will have clinically useful effects in preventing and/or treating cartilage damage, pain and/or inflammation.

Administration according to the invention method of an invention compound to a mammal to treat the diseases listed above is preferably, although not necessarily, accomplished by administering the compound, or a salt thereof, in a pharmaceutical dosage form.

The compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be prepared and administered according to the invention method in a wide variety of oral and parenteral pharmaceutical dosage forms. Thus, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be administered by inhalation, for example, intranasally. Additionally, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component an invention compound. The invention compounds generally are present in a concentration of about 5% to about 95% by weight of the formulation.

For preparing pharmaceutical compositions from the compounds of Formula I, or a pharmaceutically acceptable salt thereof, (i.e., the active component) pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations are preferred. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid

carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. Powders suitable for intravenous administration or administration by injection may be lyophilized.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from about 5% to about 70%, total, of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or

synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing an appropriate quantity of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.01 to 1000 mg, preferably 1 to 500 mg according to the particular application and the potency of the active components. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents to treat the above-listed diseases, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, are administered at a dose that is effective for treating at least one symptom of the disease or disorder being treated. The initial dosage of about 1 mg/kg to about 100 mg/kg daily of the active component will be effective. A daily dose range of about 25 mg/kg to about 75 mg/kg of the active component is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the particular invention compound being employed in the invention combination. Determination of the proper dosage for a particular situation is within the skill of the art as described above. Typical dosages will be from about 0.1 mg/kg to about 500 mg/kg, and ideally about 25 mg/kg to about 250 mg/kg, such that it will be an amount that is effective to treat the particular disease or disorder being treated.

A preferred composition for dogs comprises an ingestible liquid peroral dosage form selected from the group consisting of a solution, suspension, emulsion, inverse emulsion, elixir, extract, tincture and concentrate, optionally to be added to the drinking water of the dog being treated. Any of these liquid dosage forms, when formulated in accordance with methods well known in the art, can either be administered directly to the dog being treated, or may be added to the drinking water of the dog being treated. The concentrate liquid form, on the other hand, is formulated to be added first to a given amount of water, from which an aliquot amount may be withdrawn for administration directly to the dog or addition to the drinking water of the dog.

A preferred composition provides delayed-, sustained- and/or controlled-release of an invention compound. Such preferred compositions include all such dosage forms which produce ≥ 40% inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 3 fold the active component's ED_{40} for at least 2 hours; preferably for at least 4 hours; preferably for at least 8 hours; more preferably for at least 12 hours; more preferably still for at least 16 hours; even more preferably still for at least 20 hours; and most preferably for at least 24 hours. Preferably, there is included within the above-described dosage forms those which produce ≥ 40% inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 5 fold the active component's ED_{40} for at least 2 hours, preferably for at least 2 hours, preferably for at least 8 hours, more preferably for at least 12 hours, still more preferably for at least 20 hours and most preferably for at least 24 hours. More preferably, there is included the above-described dosage forms which produce ≥ 50% inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 5 fold the active component's ED_{40} for at least 2 hours, preferably for at least 4 hours, preferably for at least 8 hours, more preferably for at least 12 hours, still more preferably for at least 20 hours and most preferably for at least 24 hours.

The following Formulation Examples 1 to 8 illustrate the invention pharmaceutical compositions. When the formulations comprise the invention compound and a pharmaceutically acceptable carrier, diluent, or excipient, they

contain a cartilage damage treating effective amount or a therapeutically effective amount such as, for example, an anti-osteoarthritic effective amount of the invention compound. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 1

Tablet Formulation:

Ingredient	Amount (mg)
An invention compound	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

The invention compound, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed thorough a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for inhibiting cartilage damage or treating osteoarthritis.

FORMULATION EXAMPLE 2

Coated Tablets:

The tablets of Formulation Example 1 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

FORMULATION EXAMPLE 3

Injection vials:

The pH of a solution of 500 g of an invention compound and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate

is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the invention compound.

FORMULATION EXAMPLE 4

Suppositories:

A mixture of 25 g of an invention compound, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 25 mg of the invention compound.

FORMULATION EXAMPLE 5

Solution:

A solution is prepared from 1 g of an invention compound, 9.38 g of $NaH_2PO_4 \cdot 12H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 25 mg of the invention compound.

FORMULATION EXAMPLE 6

Ointment:

500 mg of an invention compound is mixed with 99.5 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 25 mg of the invention compound.

FORMULATION EXAMPLE 7

Capsules:

2 kg of an invention compound are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the invention compound.

FORMULATION EXAMPLE 8

Ampoules:

A solution of 2.5 kg of an invention compound is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg of the invention compound.

The following Formulation Examples 9 to 16 illustrate the invention pharmaceutical compositions containing an invention combination in a single formulation with a pharmaceutically acceptable carrier, diluent, or excipient. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 9

Tablet Formulation:

Ingredient	Amount (mg)
An invention compound	25
A COX-2 inhibitor	20
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	120

The invention compound or COX-2 inhibitor, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of one of the above-listed diseases.

FORMULATION EXAMPLE 10

Coated Tablets:

The tablets of Formulation Example 9 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

FORMULATION EXAMPLE 11

Injection vials:

The pH of a solution of 250 g of a COX-2 inhibitor, 500 g of an invention compound, and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 12.5 mg of COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 12

Suppositories:

A mixture of 50 g of a COX-2 inhibitor, 25 g of an invention compound, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 50 mg of the COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 13

Solution:

A solution is prepared from 0.5 g of a COX-2 inhibitor, 1 g of an invention compound, 9.38 g of $NaH_2PO_4 \cdot 12H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 12.5 mg of the COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 14

Ointment:

100 mg of a COX-2 inhibitor, 500 mg of an invention compound is mixed with 99.4 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 5 mg of the COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 15

Capsules:

2 kg of a COX-2 inhibitor and 20 kg of an invention compound are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the COX-2 inhibitor and 250 mg of the invention compound.

FORMULATION EXAMPLE 16

Ampoules:

A solution of 2.5 kg of a COX-2 inhibitor and 2.5 kg of an invention compound is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg each of the COX-2 inhibitor and the invention compound.

While it may be desirable to formulate a COX-2 inhibitor and an invention compound together in one capsule, tablet, ampoule, solution, and the like, for simultaneous administration, it is not necessary for the purposes of practicing the invention methods. A COX-2 inhibitor and an invention compound alternatively can each be formulated independently in any form such as, for example, those of any one Formulation Examples 1 to 16, and administered to a patient either simultaneously or at different times.

The following examples illustrate the invention pharmaceutical compositions containing discrete formulations of the active components of an invention combination and a pharmaceutically acceptable carrier, diluent, or excipient. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 17

Tablet Formulation of an invention compound:

Ingredient	Amount (mg)
An invention compound	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

An invention compound, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet.

Injection vial formulation of a COX-2 inhibitor:

The pH of a solution of 500 g of a COX-2 inhibitor and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the COX-2 inhibitor.

Such tablets containing the invention compound can be administered to a human from one to four times a day for treatment of the above-listed diseases, and the injection solutions containing the COX-2 inhibitor can be administered to a human 1 or 2 times per day, wherein the administration by injection is optionally simultaneous with administration of the tablets or at different times, for the treatment of one of the above-listed diseases.

FORMULATION EXAMPLE 18

Coated Tablets containing an invention compound:

The tablets of Formulation Example 17 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

Capsules containing valdecoxib or celecoxib:

2 kg of a COX-2 inhibitor are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the COX-2 inhibitor.

Such coated tablets containing the invention compound can be administered to a human from one to four times a day for treatment of the above-listed diseases, and the capsules containing the COX-2 inhibitor can be administered to a human 1 or 2 times per day, wherein the administration of the capsules is optionally simultaneous with administration of the tablets or at different times, for the treatment of one of the above-listed diseases.

Still further, it should be appreciated that the invention methods comprising administering an invention combination to a mammal to treat diseases or disorders listed above may be used to treat different diseases simultaneously. For example, administration of a COX-2 inhibitor in accordance with the invention combination may be carried out as described above to treat inflammation, arthritic pain, pain associated with menstrual cramping, and migraines, while an invention compound may be administered to treat OA or inhibit cartilage damage.

As shown above, the invention methods comprising administering an invention compound offer a distinct advantage over existing treatments for diseases such as OA that comprise cartilage damage, wherein the existing treatments modify pain or secondary symptoms, but do not show a disease modifying effect.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

All references cited above are hereby incorporated by reference herein.

Having described the invention method, various embodiments of the invention are hereupon claimed.

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